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Table of Contents on 3rd Cover

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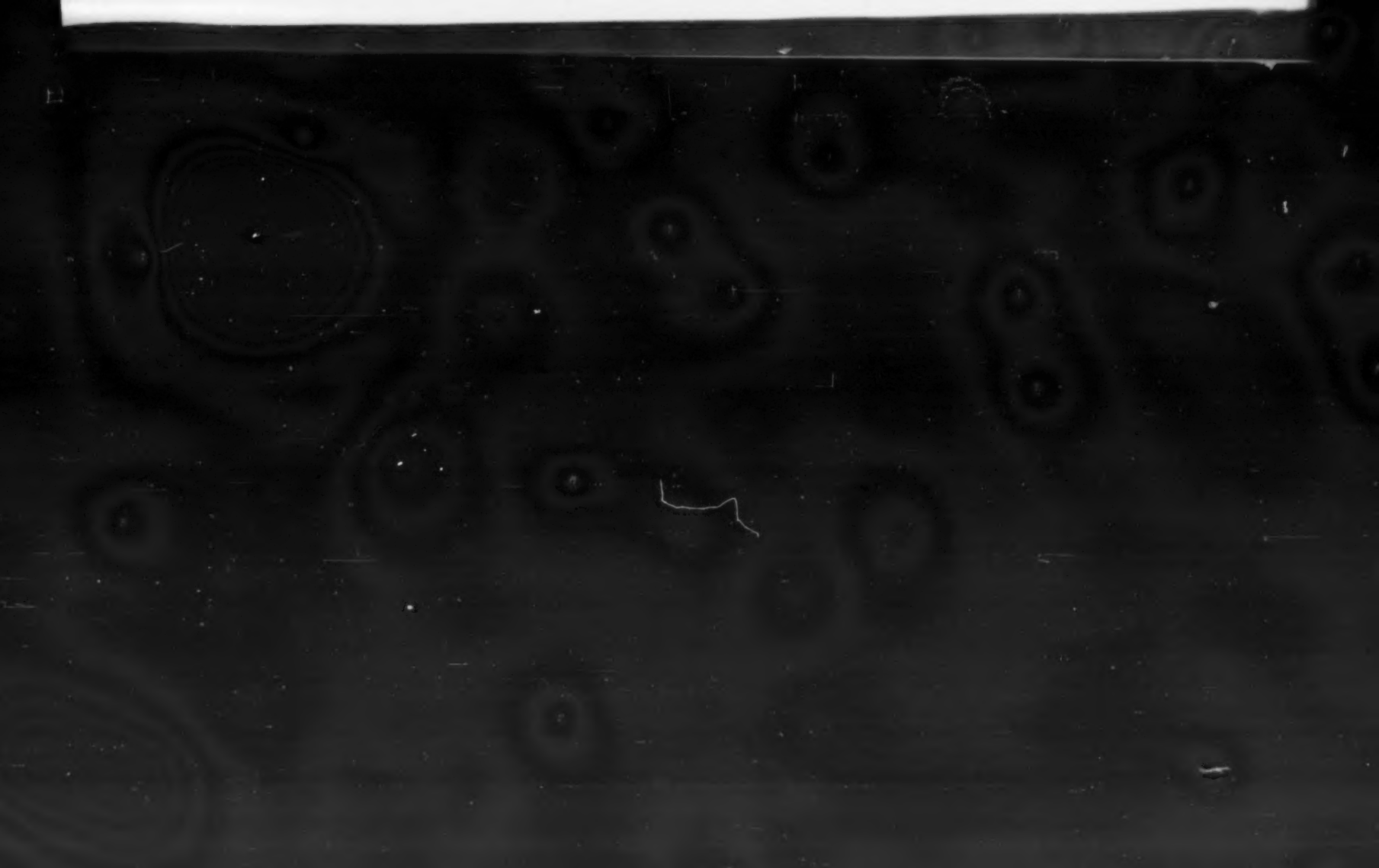

The Journal of Pediatrics

VOL. 38 JUNE, 1951 No. 6

Original Communications

SUBDURAL HEMATOMA, HYGROMA, AND HYDROMA IN INFANTS

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ABNORMALLY large quantities of subdural fluid over the convexity of the cerebral hemispheres may be termed hematomas, hygromas, or hydromas. These may be distinguished by the appearance and extent of the fluid and pathological changes in the adjacent meninges.

Clinically, their behavior is similar in that all are chronic, slowly progressive, liquid space-occupying lesions which cause diffuse pressure on the underlying brain.

The reason for distinguishing them is evident at the operating table where, following subdural punctures which satisfy the clinical criteria for subdural hematoma, some lesions are found to be hygromas or hydromas.

Ever since Hewett[24] in 1845 and Virchow[57] in 1857 described pathological changes associated with the subdural space, many authors have added information of a clinical,[12, 14, 15, 18, 19, 21, 26, 38, 46, 56, 58] pathological,[2, 7, 16, 23, 33, 34, 37] and experimental[18, 20, 25, 44, 61] nature. The reader is referred to the excellent reviews by Putnam and Cushing,[46] Sherwood,[52] and Groff and Grant.[22]

The problem of subdural hygromas is well illustrated in the collective review by Wycis[60] and other reports.[1, 36, 43]

Subdural hydromas have been described by Dandy,[10] Naffziger,[40] Da Costa and Adson,[9] Rand,[48] Brock,[4] Lichtenstein,[35] and Davidoff and Epstein.[12]

The earlier writers on subdural hematoma in infants[5, 27, 50, 52] all emphasized the diagnostic features, the value of subdural punctures, and the poor prognosis. Sherwood[52] in 1930 suggested that surgical removal of the residual neomembrane might be of value.

The surgical approach to the problem of subdural hematomas in infants was initiated by Peet and Kahn[42] in 1932 and Naffziger and Brown[39] in 1934. However, it was not until 1939 that Ingraham and Heyl,[29] by instituting a well-calculated program of subdural punctures, trephination, and radical excision, were able to report a remarkable improvement in the surgical mortality. By 1949 Ingraham and Matson[31] reported over 100 cases oper-

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ated with results that challenged the best of adult series.

In adults, the diagnosis of subdural hematoma is established by the findings at surgery or autopsy. In infants, however, the diagnosis is often considered to be established clinically by the findings on subdural puncture.

The most unequivocal diagnostic criterion found in the literature is that of Rogatz[49] who states that more than 1.0 c.c. of subdural fluid with a protein greater than 35 mg. per 100 c.c. (that of spinal fluid) is pathognomic of subdural hematoma. Ingraham and Matson[30] in their article on subdural hematoma state that more than 1.0 c.c. of subdural fluid is indicative of pathology. Elvidge and Jackson[17] state that bloody fluid indicates recent hemorrhage and xanthochromic fluid indicates old hemorrhage. Other writers simply state that the diagnosis is made by subdural puncture and go no further.

Subdural hygromas have been described as collections of bloody and/or xanthochromic fluid with or without an associated neomembrane.[1, 36, 60] This also embraces the description of subdural effusion by Penfield,[43] and Elvidge and Jackson.[17]

Subdural hydromas have been described as collections of clear or slightly xanthochromic fluid with or without a neomembrane.[4, 10, 35]

The possibility for confusion of these three terms is obvious. Indeed Kaump and Love[33] and Munro[38] relate hematoma and hygroma. Lichtenstein[35] considers hygroma and hydroma to be synonymous and differentiates them from hematoma by the absence of a neomembrane. Dandy[10] and Brock,[4] however, state that some hydromas may have an associated neomembrane, and Da Costa and Adson[9] suggest that hydromas and hematomas may be related. Discrepancies between the history and findings at operation have been noted by Ingraham and Matson,[30] Statten,[54] Kaplan,[32] and Elvidge and Jackson.[17]

PATHOGENESIS

The following is our interpretation of the many and varied theories and facts which are already recorded in the literature.

Trauma[1, 10, 34, 37, 46, 56, 60] may precipitate one or both of two primary lesions, hemorrhage,[34, 46, 56] or effusion.[1, 10] However, there are many predisposing factors such as vascular anomalies, malnutrition, and infection, as outlined by Baker,[2] Scott,[51] and Groff and Grant.[22] Trauma may be unidentifiable in which case the term spontaneous[51] may be used. In some cases, infection[36, 43] may appear to be the precipitating cause.

If the primary lesion is hemorrhage, it may be either intradural[2, 7, 16, 23] or subdural.[34, 45, 46, 56] If intradural, bleeding from intrinsic dural capillaries[2, 23] strips the mesothelial layer as a preformed membrane. The deeper layers of the dura develop an inflammatory reaction and the lesion simulates a subdural hematoma although it is still intradural.

If subdural, rupture of the pial or "bridging" veins or venous sinuses[20, 38, 45, 46, 56] gives rise to a true subdural hemorrhage which, depending upon whether or not it becomes diluted by a cerebrospinal fluid leak,[38, 57, 58] may clot early or late.

If it clots early, a relatively localized lesion is produced exciting a relatively localized dural proliferation[34] which as a neomembrane may even-

tually surround the clot to form an encapsulated hematoma. Actually, by virtue of this encapsulation the hematoma has become intradural.

If it clots late, the blood may spread extensively throughout the subdural space[17] and cause a diffuse proliferative reaction[46, 47] in the mesothelial layer of the dura and may never become encapsulated.

The progressive nature of these lesions is attributed to gradual enlargement from repeated hemorrhages,[35, 46] exudation of serum,[61] transudation of cerebrospinal fluid,[20] or by a cerebrospinal fluid leak.[1, 38, 39]

As these lesions undergo hemolysis, absorption, and dilution, the fluid changes from bloody through bloody-xanthochromic and xanthochromic to clear fluid. This is well illustrated when the process is accelerated by subdural punctures.

If the primary lesion is an effusion, it may be caused by an abnormal permeability of the arachnoid,[39] a frank arachnoid laceration[1, 10, 39] or defect,[11] as an accompaniment of cerebral edema,[10] or as a reaction to adjacent infection.[10, 43]

In any event, this fluid may have a high or low protein content; if high, the fluid may be xanthochromic and, by irritation, cause a proliferative reaction which may be called a neomembrane[9, 10]; if low, the fluid is clear and no neomembrane is present.[34]

These lesions may also increase in size by diffusion, arachnoid leaks,[1] or as inflammatory exudates secondary to adjacent foci of infection.[10, 43]

Leary[34] has emphasized a fundamental defect in the reparative powers of the dura because of its unique circulation. Ingraham and Matson[30] have emphasized the constricting effect of a fibrotic neomembrane on the rapidly growing brain.[8]

CLINICAL FEATURES

This series deals with twenty-two consecutive patients less than one year of age diagnosed as subdural hematomas from the years 1945 to 1950.

The ages on admission show an irregular distribution over the first ten months of life about which little can be said except that they are very misleading as to the actual ages of onset of symptoms. Twenty-one of the twenty-two patients had their onset of symptoms in the first four months of life. Of these, thirteen were during the first month, ten dated from the first week, including three less than one month of age on admission. Of the remainder, three had their onset in the second, two in the third, and three during the fourth months.

ETIOLOGY

Sixteen of the twenty-two patients had a definite history of prematurity, prolonged labor, abnormal presentation, difficult forceps delivery, or cesarean section. Four were reported as "normal" births, and the birth histories of two were not known.

Other types of trauma were known in three instances; all had falls with variable degrees of head injury at three, six, and seven months, respectively. The first two of these also had known birth injuries but there was no known birth history in the third.

Two cases were presented with infections which may have been causally related to the onset of the hematomas; however, one was the product of a cesarean section, and the other, while

there was no history of birth trauma, had symptoms which dated from birth.

SYMPTOMS

The most common symptom was some type of gastrointestinal upset (seventeen patients) in the form of vomiting (fifteen patients), diarrhea (three patients), or a chronic feeding problem (three patients). Eight patients had failed to gain weight normally; six of these had associated vomiting, one chronic diarrhea, and one had scurvy.

Some disturbance in the level of consciousness occurred in thirteen of the twenty-two. Six were predominantly irritable, four were lethargic, and three alternated between both.

Convulsions occurred in eleven patients; they were usually generalized tonic and/or clonic.

In three patients an abnormally enlarged head was evident prior to admission, three were grossly retarded, three had some type of respiratory irregularity with associated episodes of cyanosis, and three had episodes of fever. Miscellaneous symptoms included "colds," pallor, painful joints, blindness, deafness, etc.

This analysis emphasizes the similarity between subdural hematoma and almost any other disease of infancy.

SIGNS

While some signs were of a slightly more specific nature, none were common enough to be pathognomonic.

Some disturbance in the level of consciousness was present in fourteen of the twenty-two in the form of irritability in seven, lethargy in four, and both in three.

Enlargement of the head was either generalized (ten) or localized as frontal and/or parietal "bossing" (three). One patient had marked frontal "bossing" associated with postural occipital flattening and a relative microcephaly.

Hyperreflexia was usually generalized and was present in thirteen.

The anterior fontanel was described as "full" or "tense" in twelve patients. It is important to emphasize that the infant's head should be elevated when this observation is made.

The optic fundi were abnormal in twelve; ten showed hemorrhages of varying duration, and two showed atrophy.

Varied paresis or paralyses were present in ten patients. These ranged from bilateral sixth nerve weakness (three), nuchal rigidity (four), blindness (two), deafness (one), unilateral facial weakness (two), and hemiparesis (four). These signs were of no localizing value and most disappeared following subdural punctures.

Retardation was evident in seven of the twenty-two. Malnutrition was fairly marked in five. Infection of various types was present in thirteen and anemia occurred in twelve.

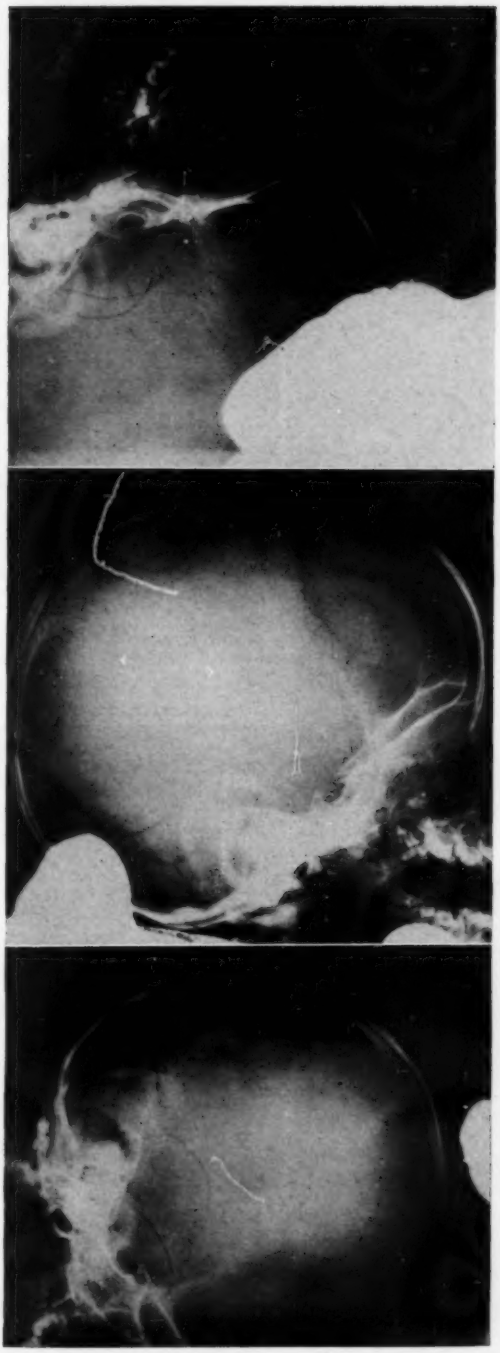
One patient had multiple healed fractures of long bones similar to those described by Caffey.[6]

These signs point to significantly increased intracranial pressure with a variable degree of impairment of cerebral function.

SPECIAL STUDIES

These included subdural and spinal punctures, x-ray studies, and electroencephalograms.

The technique of subdural puncture has been clearly described by Ingraham and Matson[30] and will not be repeated. We routinely give penicillin,

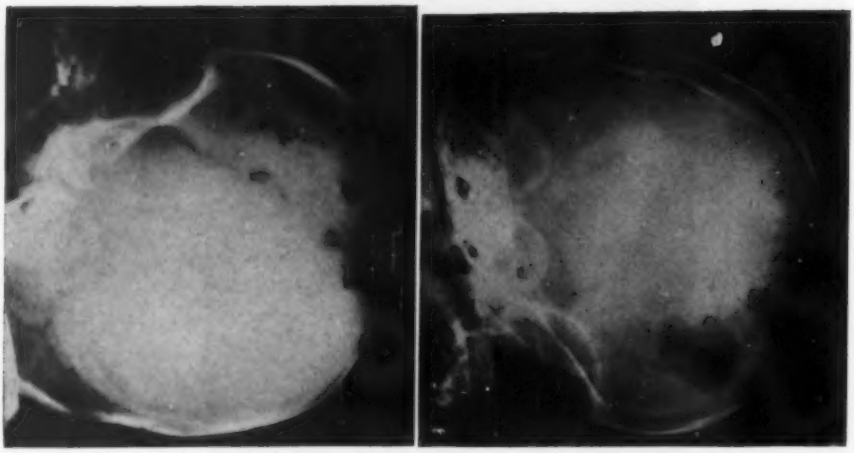


A.

B.

C.

Fig. 1.—Chronic subdural hydroma showing subdural oxygen which moves freely from frontal to occipital poles with head in *A*, face up, *B*, erect, and *C*, face down positions. Note: By x-ray this condition is indistinguishable from chronic subdural hygroma.



A. *B.*

Fig. 2.—Chronic subdural hematoma showing a localized collection of subdural oxygen in the frontal region. *A*, face up position; *B*, face down position.

A. *B.*

Fig. 3.—Pneumoencephalogram, showing apparent cerebral and cortical atrophy before operation. Note: The falx is not outlined and cortical markings extend to periphery. *A*, Preoperative study after subdural spaces had been tapped dry and where a chronic encapsulating membrane containing a small amount of xanthochromic fluid was found. *B*, Postoperative study on same patient. Note the normal cortical markings and the relatively dilated third ventricle. The apparent cortical atrophy is no longer evident but there is some residual cerebral atrophy.

and the subdural punctures are extended over a longer period of time in the attempt to "dry up" the subdural spaces.

Of our twenty-two patients, twenty-one had subdural punctures and one had a ventriculogram. Of the twenty-one, fifteen were bilaterally positive and six were unilaterally positive; one was bilaterally clear, five bilaterally xanthochromic, six bilaterally bloody-xanthochromic, four unilaterally xanthochromic, two unilaterally bloody-xanthochromic, and three were mixed bilaterally.

Spinal punctures were done in twenty patients of whom seventeen showed clear fluid, three were bloody, and two were not reported. Six of those with clear fluid showed protein values between 40 and 90 mg. per cent.

Oxygen was injected following subdural punctures in nine patients and showed the subdural space in every case. In most instances, this oxygen moved freely throughout the subdural space with appropriate positioning of the head (Fig. 1). This, incidentally, is inconsistent with the usual concept of a discrete encapsulated chronic subdural hematoma (Fig. 2). In a few cases subarachnoid oxygen was also evident indicating an arachnoid leak.

Pneumoencephalography was done in seven cases without any untoward effects. In all it showed varying degrees of prominent surface spaces (Fig. 3*A*), and in some the subdural space was also filled (Figs. 4 and 5).

A ventriculogram done in one patient did not afford any abnormal x-ray findings.

Skull films were negative except in six patients where widened sutures were reported and two where occipital flattening was noted. Their chief value was in excluding fractures, ectopic calcifications, and other bony anomalies. Of four patients with enlarged heads, tense fontanels, and abnormal fundi, two showed widened sutures and two did not.

Electroencephalographic findings were of little aid in diagnosis.

Fig. 4.—Pneumoencephalogram showing bilateral filling of the subdural spaces in the erect position.

DIAGNOSIS

The diagnosis of "subdural hematoma" was made by subdural and spinal punctures in twelve of the twenty-two cases. All showed bloody and/or xanthochromic subdural fluid in the presence of spinal fluid with a normal protein.

The demonstration of a dilated subdural space by oxygen injection led to the diagnosis in six patients one of whom had clear subdural and spinal fluids. All of the remaining five had bloody and/or xanthochromic subdural fluid with clear spinal fluid with an elevated protein in three, and grossly bloody fluid in two.

Three cases were diagnosed by their response to subdural punctures; two

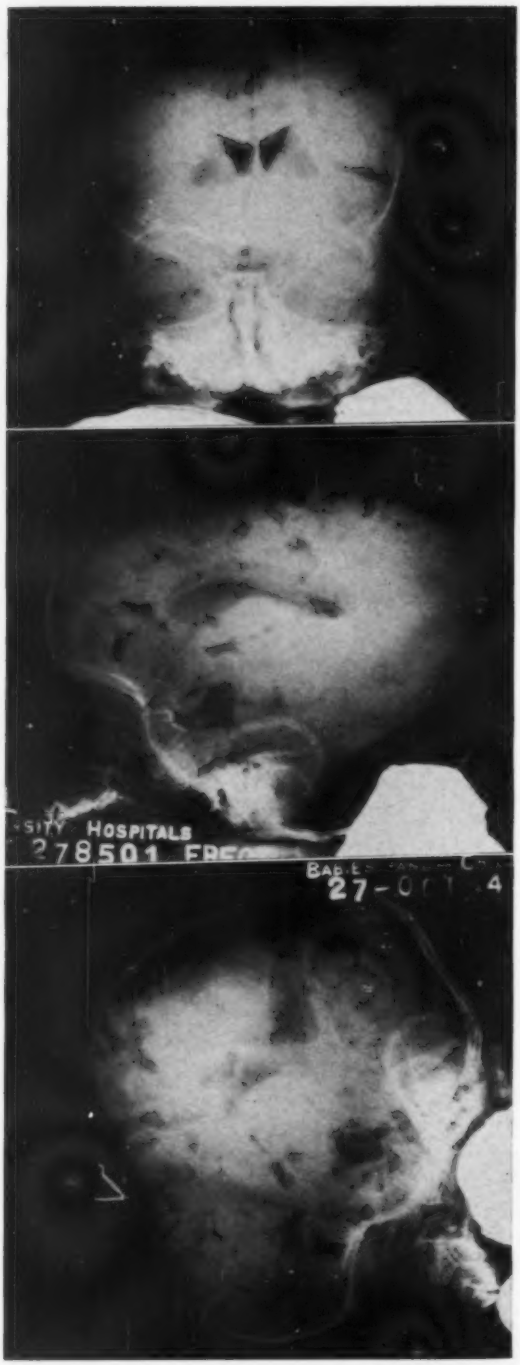


Fig. 5.—Pneumoencephalogram showing oxygen entering the subdural spaces and moving freely from frontal to occipital poles with appropriate changes in position. *A*, Anteroposterior view with infant lying on left side; *B*, lateral view with infant erect; and *C*, lateral view with face down.

had bloody and/or xanthochromic subdural fluid in the presence of clear spinal fluid and one had both bloody subdural and spinal fluids. In this last patient, the tense fontanel became soft, the infant relaxed, and thereafter became progressively more able to retain feedings.

One case was diagnosed in the course of postparietal trephination for ventriculography.

The diagnosis actually established was an abnormal collection of subdural fluid. The oxygen studies are of considerable interest in that while they demonstrate a dilated subdural space they also show that this is frequently a diffuse and not a localized dilatation. They also show that there frequently are communications between the subarachnoid and subdural spaces. These findings suggest that some cases we called subdural hematomas were actually hygromas or hydromas.

DIFFERENTIAL DIAGNOSIS

This includes five conditions which have either abnormal surface collections of fluid or subcortical collections with an overlying "paper-thin" cortex.

Abnormal surface collections of fluid may occur in an external absorptive hydrocephalus or with a focal cortical atrophy overlain by a relatively localized "subarachnoid lake."

There may be marked thinning of the cortex so that intraventricular or subcortical fluid may lie only a few millimeters beneath the dura. This may occur with an obstructive hydrocephalus, congenital porencephaly, atrophy, or intracerebral cyst associated with tumor or hemorrhage.

Focal atrophy or porencephaly may be accompanied by static focal neurological signs, whereas signs of pressure or meningeal irritation are absent.

A tumor may present signs of increased intracranial pressure with a localized progressive neurological deficit.

Intracerebral hemorrhage may cause fulminating localizing signs, increasing pressure, and meningeal irritation.

The various types of hydrocephalus may require an air study for diagnosis.

It is important to realize that the same injury which initiated the subdural bleeding may also have caused a cerebral contusion, subarachnoid hemorrhage, or may have irreparably damaged the brain itself. The effects of sustained compression may also cause permanent damage to the brain. A collection of subdural fluid may obscure the signs of coexistent intrinsic disease so that after maximal recovery with subdural punctures has occurred, the case should be re-evaluated, if necessary, employing an air study.

SURGICAL CONSIDERATIONS

Degrees of malnutrition or anemia tolerated by an older child may be devastating to an infant. Cryptogenic infection of even mild degree can cause a greater general disturbance. Hemorrhagic tendencies may be more insidious and difficult to control, especially in the presence of fever or infection.

Following the several weeks of management on the Pediatric Service, during which time the subdural space is decompressed as completely as possible by alternate daily punctures, these patients are usually in optimum condition for surgery.

With thorough subdural punctures the problem is no longer one primarily

of relieving acute pressure on the brain but rather of preventing the late effects of chronic pressure either by a constricting membrane or a chronic collection of subdural fluid. This means that surgery aims at (1) removing the membrane as completely as possible, and (2) preventing the reformation of the subdural fluid.

In the past, we have employed both simple trephination and radical osteoplastic flaps; however, the results were not altogether satisfactory. Subdural fluid tended to recur and frequently required extended postoperative aspiration. In two patients reoperation was necessary for removal of the reformed membrane.

During the past year, therefore, we have allowed ourselves to be guided primarily by the history of a proved collection of subdural fluid and have routinely turned bilateral parietal osteoplastic flaps.

The right side is done first unless the volume of subdural fluid on the left is very much greater, and this is followed in one to two weeks by a

Fig. 6.—Chronic neomembrane (inner aspect) showing fibrous tissue with a mesothelial border on each side.

Fig. 7.—Minimal neomembrane showing fibromesothelial proliferation in the inner layer of the dura.

similar procedure on the opposite side. Transfusion during operation is routine.

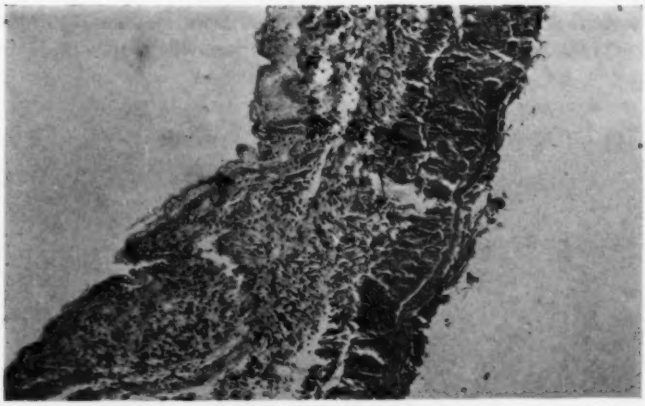


Fig. 8.—Neomembrane densely adherent to the outer collagenous fibers of the dura.

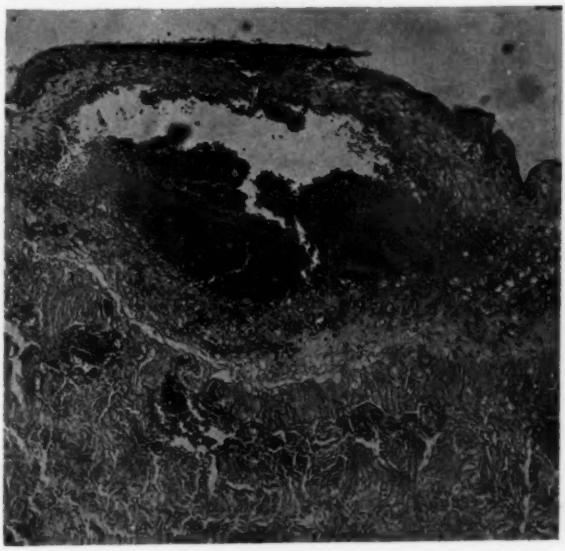


Fig. 9.—Neomembrane with intrinsic hemorrhage (intradural hematoma). The superficial and deep capillary plexi and the deep collagenous fibers of the dura are evident.

The skin incision averages 5 cm. in diameter. It is placed behind the hairline with its base toward the ear. The bone is penetrated with a small perforator and cut with scissors on the Gigli saw. Care is taken to avoid the coronal suture and anterior fontanel. The bone flap is turned down with a hinge of temporal muscle.

The dura is usually tense but frequently is not discolored. It is turned back as a flap with the base toward the sagittal sinus.

Upon opening the dura, any of four situations may be encountered.

1. Bloody and/or xanthochromic fluid may be found encapsulated by a brownish translucent membrane which forms a discrete sac over the convexity of the fronto-parieto-temporal region. Here removal of the fluid and the sac

Fig. 10.

Fig. 11*A*.

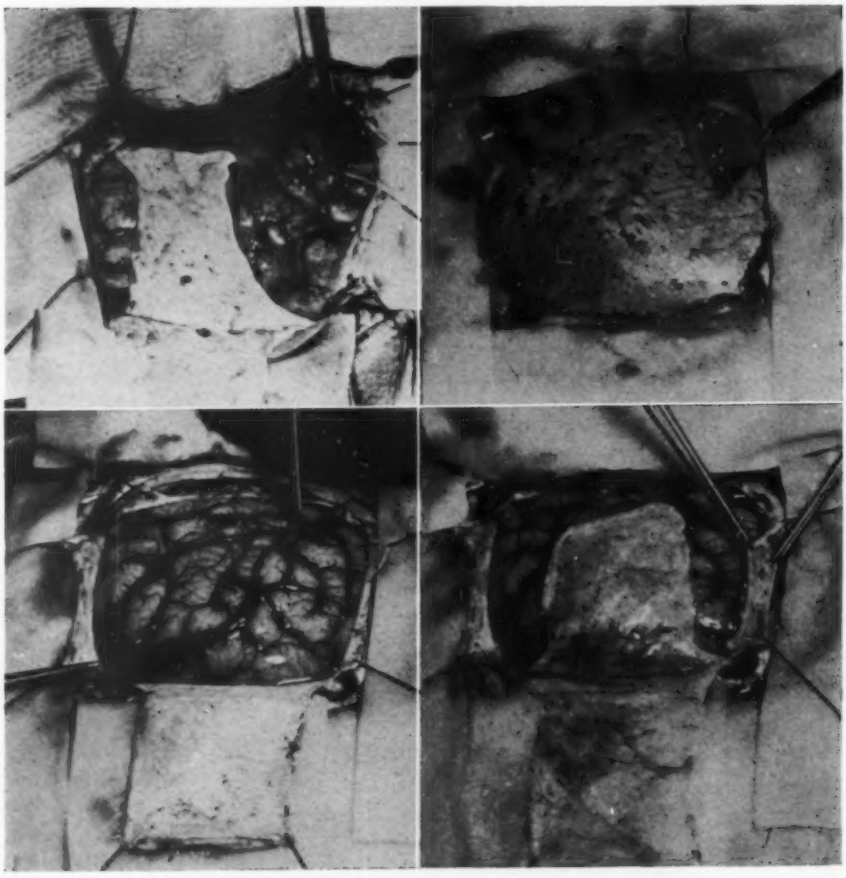


Fig. 11*B*.

Fig. 11*C*.

Fig. 10.—Operative field showing the apparent cortical atrophy, the space between brain and skull, the frail neomembrane adherent to the inner surface of the dura, and the reflected "mesothelial" layer stripped from the dura.

Fig. 11.—Operative fields showing artificial separation of the dural layers: *A*, on preliminary opening of the dura; *B*, dural flap turned down revealing prominent "lakes" of subarachnoid fluid; and *C*, showing the mesothelial layer of the dura reflected upward and beginning separation at the margin. Note: This is the case of chronic subdural hydroma, and the apparent neomembrane in *A* is really the "mesothelial" layer. See Fig. 12.

is a relatively straightforward procedure. We have employed the term chronic subdural hematoma in this situation.

2. Xanthochromic fluid overlying a brownish-gray fibrous membrane (Fig. 6) bridging the concavity of the frontoparietal-temporal region and constricting the underlying brain. When incised, the margins of this membrane spread and the cortex herniates through the opening with danger of rupture. This poses a more difficult problem in removal. We have used the term chronic subdural hematoma in this situation.

a part. This membrane is physically incapable of encapsulating the fluid found or of constricting the brain. It might very easily be missed through a trephine opening. These cases we have described as subdural hygromas.

Here we have found it most satisfactory to develop a plane of cleavage in the dura itself and to literally strip its inner "mesothelial" layer (Figs. 10 and 11). While this is a difficult task in a normal dura in these cases, the inner mesothelial and outer endocranial layers separate unusually easily. This "mesothelial" layer with its adherent neomembrane is removed

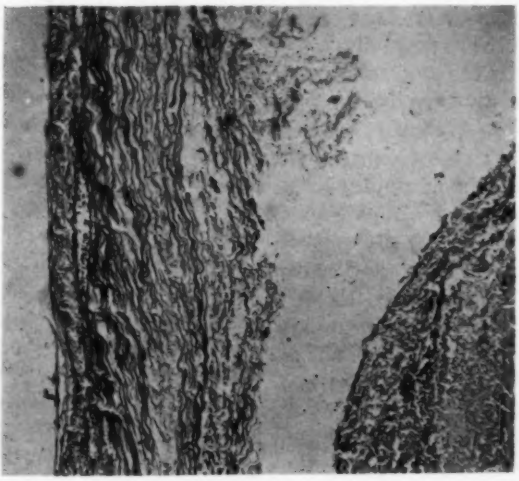


Fig. 12.—Normal dura showing only questionable edema. From a case of subdural hydroma.

3. Xanthochromic fluid free in the subdural space with a frail subdural membrane which may appear as a dull brown deposit on the inner surface of the dura (Fig. 7) or as a very fragile transparent brown membrane more or less adherent to the dura (Figs. 8 and 9). In either case this membrane tends to shred and is very difficult to remove from the dura of which it seems to be from all the accessible concavity of frontal, parietal, and temporal regions.

In some cases this cleavage plane disappears over the frontal region anteriorally and the occipital region posteriorally where the mesothelial layer will tend to shred rather than strip. In other cases its limits are not found where they extend beyond the line of vision on to the falx, tentorium,

and floor of the anterior and middle fossae.

The "raw" endocranial dural surface which remains is less of a problem in hemostasis than the surface left if the neomembrane is torn or scraped away.

4. Clear or slightly xanthochromic fluid with no apparent neomembrane. Here we have stripped the inner dural layer bilaterally in one patient and have found no significant pathological changes (Fig. 12). This case has been described as a subdural hydroma although no arachnoid leak was demonstrated.

With each of these four situations there usually is a space of a centimeter or two between skull and brain which had been occupied by the subdural fluid. The arachnoid is transparent and usually contains prominent "lakes" of subarachnoid fluid lying in widened sulci between atrophic gyri. The surface cerebral vessels may be unusually tortuous where they course through these subarachnoid "lakes." When one sees these prominent subarachnoid "lakes" (Fig. 10) one is reminded of Penfield's[43] speculation concerning obstruction to the cerebrospinal fluid exit and its relation to hydrocephalus.

We routinely drain these "lakes" by multiple arachnoid incisions to allow the escape of cerebrospinal fluid rather than decompress the ventricle to facilitate the exposure.

OPERATIVE STATISTICS

In the seventeen patients treated surgically there were thirty operations, twenty-five osteoplastic flaps, and five trephinations. There were ten bilateral and five unilateral flaps of which one was a reoperation for recurrence of a hematoma five months postoperatively.

One of the flaps became infected and healed with a local revision two months later. One was reopened forty-eight hours postoperatively for a secondary epidural hemorrhage. A few of the more recent cases developed 10 to 20 c.c. of fluid beneath the scalp which responded to one or two aspirations. One early patient died on the operating table and in this case had not been systematically decompressed by subdural punctures preoperatively. It is of interest that this infant at autopsy showed bilateral hygromas with delicate neomembranes which covered the entire inner surface of the dura above the tentorium.

One patient had bilateral and three had unilateral trephination. One of the latter was negative for any subdural fluid although this had been proved preoperatively by serial punctures. The remainder required postoperative aspiration of the scalp for several weeks, and one who had bilateral trephination returned one month postoperatively for reoperation for a recurrence.

There were five bilateral chronic subdural hematomas, five bilateral hygromas, and one bilateral hydroma. One had a chronic hematoma on one side and a hygroma on the other. Four had unilateral hygromas of whom one has recently recurred two years postoperatively for removal of a laminated chronic hematoma from the other side.

It is of interest to re-examine the symptoms and signs on the basis of these findings.

Bilateral chronic hematomas showed a higher incidence of irritability, convulsions, abnormal fundi, enlarged

head, tense fontanel, and bloody xanthochromic subdural fluid on initial examination.

Bilateral subdural hygromas showed a higher incidence of vomiting, malnutrition, failure to gain weight, and xanthochromic subdural fluid on initial examination.

In every case where the subdural space was shown by oxygen studies to be diffusely dilated the surgical finding was a hygroma. Where the subdural dilatation was localized a chronic hematoma was found. Diffuse dilatation was also evident in the case diagnosed at operation as a hydroma.

RESULTS

In discussing the results, it is well to bear in mind that most patients show marked improvement during the course of subdural punctures. Surgery aims primarily at consolidating the ground gained by (1) preventing reformation of the fluid and/or the neomembrane, and (2) permitting the resumption of a normal mental and physical development. Hence the results may be evaluated as immediate (depending upon symptomatic relief) and remote (depending upon a normal mental and physical development).

Of the twenty-two patients, five were treated by subdural punctures alone and of these one is mentally retarded, one is hydrocephalic, two could not be followed, and one is awaiting surgery.

Of the remaining seventeen patients who were operated upon, one is dead, one had a negative trephine, and one is hemiplegic and retarded.

Three are only fair results in that retardation, in spite of subdural punctures prior to surgery, has not improved satisfactorily.

Eleven of the seventeen are considered good results; however, three have been followed for less than six months.

The over-all results then include thirteen good results, two fair, three poor results, one death, and three are not known.

COMMENT

One of the main purposes of this paper has been to illustrate the multiplicity of pathological findings which may be associated with abnormal collections of subdural fluid.

In describing these findings we have used the terms "chronic subdural hematoma" to indicate bloody and/or xanthochromic fluid encapsulated by a well-defined neomembrane; "hygroma" to indicate a collection of xanthochromic fluid free in the subdural space with a nonencapsulating neomembrane; "hydroma" to indicate a collection of colorless or slightly xanthochromic fluid free in the subdural space with no evidence of a neomembrane.

The merit of these distinctions is in their use as descriptive labels for the gross pathology found at operation and they carry with them specific implications as to treatment.

It is our impression that they all may represent stages in healing of subdural or intradural hemorrhage, and that birth trauma is the most common precipitating factor. Trauma at birth may explain the high incidence of bilateral findings.

The problem of what constitutes "normal" trauma to the infant's head during birth has never been adequately defined. In the adult, bloody spinal fluid is invariably an abnormal finding, but in the newborn infant, it is

TABLE I

Case Number		1	2	3	4	5	6	7	8	9	10
Hospital Number		247 530	256 847	261 115	261 645	264 930	267 916	270 945	275 932	275 561	278 501
Birth Injury[1]		P	DL	B	?	DL	DL	?	DL	PP	B
Age on Admission[2]		8M	6M	4M	5M	4D	3M	7M	2M	1D	6M
Duration of Symptoms[2]		4M	6M	1M	2M	5D	3M	1D	2D	1D	6M
Symptoms	Feeding problem	1									
	Vomiting	1	1		1	1	1				
	Diarrhea										1
	Failure to gain weight										1
	Lethargy		1			1	1	1		1	1
	Irritability	1			1		1		1		
	Convulsions	1	1	1	1			1			
Signs	Enlarged head	1	1		1				1	1	1
	Tense fontanel	1			1	1	1	1	1	1	1
	Retinopathy	1	1		1			1	1		1
	Irritability	1		1	1		1	1			
	Hyperreflexia	1			1		1			1	1
	Paralysis	1*		1*				1*		1*	1*
	Lethargy		1			1	1	1			
	Retardation				1						1
	Malnutrition										
	Anemia		1		1			1	1		1
	Infection		1	1	1		1	1			
Subdural Punctures[3]											
	Right	X			BX	B		BX	C		X
	Left	BX		X	BX	BX	BX	BX	C	X	BX
Spinal Punctures[3]											
	Color		C	C	C	B	B	B	C	C	C
	Protein		N	N	N		N		89	88	58
X-rays[4]	Wide sutures	–	+				–	–	–	+	+
	Subdural space		G		L			L	G		L
	Atrophy								+		+
Operative Findings[5]											
	Right	Hem	Hyg		Hem			Hem			
	Left	Hem		Hyg	Hem		Neg	Hem			
Results[6]	Immediate	F	F	D	P	G	?	F	?		
	Remote	G	G	D	P	?	?	G	?	P	P
	Duration	5Y	4Y		3Y			2Y		2Y	2Y
Miscellaneous * = Indicates location of paralysis noted above		*Left leg		*Left arm			Blind; stiff neck	*Left face		*Left E.O.M.	*Bilat. 6th; blind; stiff neck; Front; long lesion

[1] *Birth Injuries*
P = Premature.
B = Breech.
PP = Persistent posterior.
DL = Difficult labor.
CS = Cesarean section.
N = Normal.

[2] *Ages*
D = Days.
M = Months.
Y = Years.

[3] *Punctures*
B = Bloody.
BX = Bloody-xanthochromic.
X = Xanthochromic.
C = Clear.
N = Normal protein.

ANALYSIS OF CASES

11	12	13	14	15	16	17	18	19	20	21	22	Totals of the 22 Cases	Bilateral	
275	281	286	279	279	283	288	295	292	288	294	295		Hematoma	Hygroma
188	991	434	082	952	043	689	504	748	108	252	097			
PP	P	P	N	N	P	PP	N	DL	N	CS	P			
2M	6M	7M	10M	9M	8M	7M	1M	10M	6M	4M	8M			
2M	2M	7M	10M	7M	8M	7M	1M	8M	6M	2D	6M			
1					1							3	1	1
1	1		1	1	1	1	1		1	1	1	15	3	5
		1					1					3	1	0
1			1		1	1	1	1			1	8	0	3
1	1									1		9	2	1
	1							1				7	3	0
1	1	1	1	1						1		11	5	3
1	1	1		1		1	1	1			1	14	4	2
1		1		1						1		12	4	2
1	1	1	1		1		1					12	5	2
			1		1		1	1				10	3	2
1	1	1			1	1	1		1	1		13	4	3
1*		1*		1*				1*	1*			10	3	1
				1			1			1		7	1	2
		1	1		1	1		1				7	2	3
			1		1	1	1				1	5	0	3
1	1	1			1	1		1	1			12	4	2
1	1		1		1	1	1	1		1		13	3	4
X	BX	BX	BX	X	X	X		X		X	X	4BX } 90%	1BX } 30%	
BX	BX	BX	BX	X	X	B	X	X	X	X	X	5BX }	2BX }	
C	C	C	C	C	C	C	C	C	C	C	C			
58	N	50	N	108	N	54	N	N	N	N	N			
+	+	+		−	−	−		−	+	−	−			
L		L	G	G	G	G			G		G			
	+		+		+	+								
Hem	Hem Hem	Hem Hem	Hyg Hyg	Hyg Hyg	Hyg Hyg	Hyg Hyg		Hyg Hem	Hyg	Hyg Hyg	Hyd Hyd	17	5	5
G	G	F	G	F	G	G	G	G	G	G	G	13G 2F		5G
G	G	F	G	F								3P 1D	3G	
2Y	1Y	1Y	1Y	1Y	9M	9M	3M	6M	6M	3M	3M	3?	1F	
													1P	
*Rt. hemiparesis		*Bilat. 6th	Stiff neck	*Bilat. 6th			Arthritis; pyelonephritis; septicemia	*Rt. arm	*Rt. face	Deaf; pneumococcal meningitis	U.R.I.			

[a] *Subdural Space*
G = Generalized dilatation.
L = Localized dilatation.

[b] *Operative Findings*
Hem = Hematoma.
Hyg = Hygroma.
Hyd = Hydroma.

[c] *Results*
G = Good.
P = Poor.
F = Fair.
D = Died.
? = Not known.

often considered of little clinical significance.[3, 55] The clinical evidence of the effects of this trauma is obscured by the lag in functional development of the cerebral hemispheres.[25, 55]

These factors may explain discrepancies in correlating birth injuries, duration of vague symptoms, and ages of admission to hospital.

Many of these infants apparently did well in spite of their traumatic births and then days, weeks, or months later developed an insidious pattern of nonspecific symptoms such as feeding problems, failure to gain in weight, mental retardation, irritability, lethargy, etc., and when these progressed to intractable vomiting or convulsions, they were hospitalized for study.

Others were admitted because of infections such as otitis media, pneumonitis, and arthritis. These patients frequently had a history of diminished resistance to infections and their subdural fluid showed a degree of xanthochromia indicative of a chronic process. This makes one wonder whether chronic collections of subdural fluid might predispose these handicapped infants to infections which they might otherwise ward off.

Some were admitted with a nonspecific history of failure to gain weight, etc. until after a relatively minor fall they suddenly developed convulsions, coma, or intractable vomiting. Here also, when one finds subdural fluid with a marked degree of xanthochromia, one wonders whether the fall was the cause or an effect of the subdural lesion.

The most significant findings on initial examination are those of a chronic increase in intracranial pressure such as an enlarged head, widened sutures, or pressure markings on x-ray and delayed closure of the fontanel, or those of a recent increase in intracranial pressure, such as a tense fontanel and retinal hemorrhages. However, as Ingraham and Matson[30] have pointed out, it is important to suspect the presence of subdural fluid as this will lead to subdural puncture.

The purpose in doing a subdural puncture is to establish the presence or absence of subdural fluid in abnormal amounts. This fluid may be bloody suggesting a hematoma, xanthochromic suggesting a hygroma, or clear suggesting a hydroma.

The response of the infant to the puncture may be more important than the appearance of the fluid, and here we would like to repeat Ingraham and Matson's[30] comment that this is the beginning of treatment.

Whatever the appearance of the subdural fluid, a spinal puncture should also be done for comparison. If the spinal fluid is bloody and/or xanthochromic, serial subdural and spinal punctures will be necessary for evaluation.

In those cases in which there is any element of doubt, the subdural fluid should be replaced by oxygen and x-rays taken with the head in the erect, face up and down, and lateral positions. This should not be done, however, until the subdural fluid has been greatly diminished by punctures. A localized dilatation of the subdural space will indicate a hematoma, a generalized dilatation will suggest a hygroma if the fluid is xanthochromic, or a hydroma if the fluid is clear.

In some cases simultaneous visualization of the subdural and subarachnoid spaces will indicate an arachnoid leak but this does not exclude the presence of a neomembrane.

If the infant does not make a satisfactory recovery during the course of subdural punctures, it may indicate irreparable damage to the brain or a coexisting lesion which may also be treated. For this reason, although the diagnosis of hematoma, hygroma, or hydroma has been established, a pneumoencephalogram may be necessary to completely evaluate the patient.

Unless an unusually massive acute hematoma necessitating heroic surgery is present, these lesions can be controlled by subdural punctures as long as the fontanel is patent.

The futility of simply draining the subdural fluid by one puncture is evident by its rapid reformation on subsequent punctures. This suggests that while the bulk of the fluid causes the symptoms, it is itself an effect of the associated pathology in the meninges.

Surgery aims at removal of the fluid, removal of the neomembrane, and disrupting any "flap valve" effect of an arachnoid tear.

Unless the lesion is a chronic encapsulated subdural hematoma, the neomembrane may be missed through a single trephine opening and therefore we feel that an osteoplastic flap is preferable. If the lesion is a hematoma its complete excision is desirable; if a hygroma, we recommend stripping the inner "mesothelial" layer of the dura; if a hydroma, it may simply suffice to make multiple arachnoid incisions as Dandy[10] has suggested.

We feel that further improvement in the results may be gained by alerting ourselves to the frequency of hygromas and hydromas as well as hematomas. The warning history of a traumatic birth and nonspecific symptoms during the first month or two of life where there is any suggestion of intracranial pressure should warrant an exploratory subdural puncture.

Some of these lesions may heal spontaneously and some may recur after a considerable latent interval. Since the time factors of healing are not well understood and the brain is rapidly growing, we do not like to delay surgery. However, we do feel that it is possible to operate too early.

SUMMARY

1. The various diagnostic criteria for subdural hematoma, hygroma, and hydroma have been briefly reviewed.

2. The various theories of pathogenesis are drawn together into an inclusive review.

3. Twenty-two cases are analyzed from the standpoints of incidence, symptoms, signs, special studies, operative findings, pathology, and results.

4. The diagnostic criteria for chronic subdural hematoma, hygroma, and hydroma have been defined in a mutually exclusive manner. Their diagnostic procedures and individual treatment are mentioned.

5. The significance of birth injuries, neonatal "silent period," and duration of nonspecific symptoms is emphasized.

6. A definitive surgical treatment for subdural hygroma is described.

7. The relative frequency of hygroma and hydroma is mentioned.

8. The importance of evaluating concurrent intrinsic brain damage prior to operation is emphasized.

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ABDOMINAL PAIN AS A MANIFESTATION OF EPILEPSY (ABDOMINAL EPILEPSY) IN CHILDREN

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IT IS generally known that abdominal or epigastric pain is a frequent aura of an epileptic seizure. Gowers,[1] in 1901, analyzed the case histories of over 2,000 epileptic patients and found abdominal pain to be the most common aura. Patrick and Levy[2] found attacks of abdominal pain to be a "forerunner" of grand mal seizures in thirteen out of 500 cases. Bridge,[3] in his study of 742 epileptic children, also found abdominal complaints to be the most common of the aura.

In 1941, Klingman and co-workers[4] studied a small group of children with abdominal pain, both clinically and with the electroencephalograph, and inferred that the abdominal pain in these children was related to epilepsy. Hoefer, Cohen, and Greeley[5] just recently reviewed studies on thirty-one children with complaints of episodic, paroxysmal abdominal pain considered to be of cerebral origin.

Although abdominal pain has been known to be associated with epilepsy as far back as Hughlings Jackson, the syndrome of "abdominal epilepsy" seems to have been first described by Moore[6] who reported his initial case in 1944, and since[7] then has studied eighteen additional cases.

MATERIALS AND METHODS

The present report deals with clinical and electroencephalographic studies on fourteen children who suffered with recurrent paroxysmal attacks of abdominal pain. Each patient was studied intensively to eliminate other causes for the pain.

The age of the patients at the time they were first seen by us varied from 5 to 11 years. One patient was seen at the time of the occurrence of his first pain, three had been suffering with pain for nine months, two for one year, five for eighteen months to two years, and three for over two years.

The abdominal pain was periumbilical in location, but did radiate in some instances to the epigastrium. It always occurred very suddenly and was very severe and colicky in character. In eight patients, the pain lasted for five to ten minutes, in three from thirty to forty-five minutes, and in three the pain lasted twenty-four to thirty-six hours. In each instance the pain was immediately followed by postictal-like exhaustion and sleep. Associated gastrointestinal symptoms, such as nausea and vomiting, were present in eight patients. Four complained of nausea at the onset of the pain, and four vomited two to three times during the course of the pain.

Frank convulsions were not present in any patient at the time they were first seen by us. There was a family history of epilepsy in only two of the twelve cases.

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ELECTROENCEPHALOGRAPHIC STUDIES

Electroencephalographic studies revealed definite abnormalities in eleven cases, and normal brain wave patterns in three patients. An analysis of the abnormal electroencephalographic findings showed four patients with abnormally fast waves for their age; four with abnormally slow waves; one with paroxysmal burst of spikes; and one showed high voltage slow spike and wave forms. One patient revealed a slow wave focus with a marked generalized build-up. With the exception of one patient (R.O.), the cerebral electrical abnormalities were present at the time the patients were asymptomatic (free of pain). An electroencephalographic tracing was obtained on R.O. at the time he was having an attack of abdominal pain.

ANTICONVULSANT THERAPY

All fourteen patients have been or are being treated with Dilantin. In three patients, the Dilantin was discontinued after six months because the drug proved to be ineffective. In the remaining eleven patients, the abdominal pains have been completely controlled with this drug.

The three patients who did not respond to the Dilantin were also previously treated with phenobarbital without benefit. Two of these patients are now treated with 5-phenyl, 3-methyl hydantoin (Nuvarone) and one with Mesantoin. Sufficient time has not yet elapsed to determine the efficacy of these latter drugs.

CASE REPORTS

For the purpose of this presentation, the case histories and the electroencephalographic tracings of four exemplary patients are presented. A four-channel and an eight-channel Offner electroencephalograph were used to perform the tests. All of the tracings shown in Figs. 1 to 8 are scalp-to-ear leads taken during the resting state.

CASE 1.—R. C. is a 9-year-old white boy who weighed 7 pounds, 8 ounces following a normal birth. Infant and childhood development were normal.

About four years ago, he began having "cramping pains in the stomach" and continued to have these "cramping pains" periodically until 7 years of age, at which time he was first seen by us. The abdominal pains were characterized by severe, constant, cramplike pains localized to the periumbilical area. They always occurred between 3 A.M. and 6 A.M. and would awaken him from sleep. He usually vomited once or twice at the onset. The pain usually lasted from fourteen to forty-five minutes and was always followed by a deep sleep. It recurred one to two times a month, but between attacks, he was asymptomatic, active, and felt well. He had had no frank convulsions in the past.

At 6 years of age, he had an exploratory laparotomy because of the abdominal pain. A normal appendix was removed, and no pathological conditions were found to account for the pain.

When first seen by us, physical examination revealed a well-developed and well-nourished 7-year-old white male. He was cheerful, cooperative, and intelligent, and gave the appearance of a well-adjusted young boy. His general examination, including neurological, was completely negative.

He was examined completely for all of the usual causes of abdominal pain, including an intravenous pyelogram and gastrointestinal barium studies, with completely negative findings. A routine electroencephalogram (Fig. 1) revealed an abnormal brain wave pattern with abnormally slow, relatively high voltage, three to four

Fig. 1.—Sample of EEG of R. C. The patient was asymptomatic at this time.

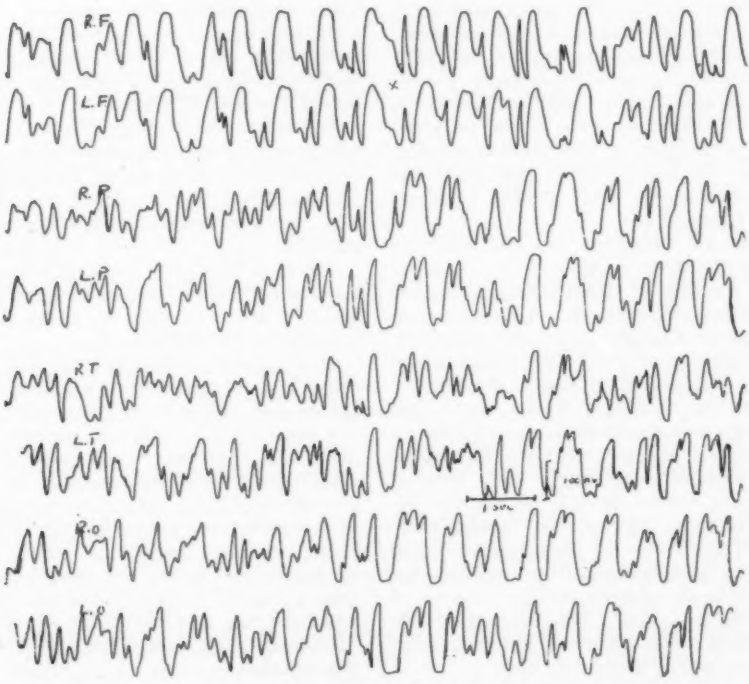

Fig. 2.—Sample of EEG of J. M. The patient was asymptomatic at this time.

per second waves. The abnormally slow waves were present in all leads.

He was given 32 mg. of phenobarbital three times a day. The abdominal pains persisted, and the phenobarbital was increased over the course of the subsequent four months to a maximum of 64 mg. four times a day, without benefit. The phenobarbital was discontinued at this time, and he was then started on 100 mg. of Dilantin three times a day. He has been seen by us at regular intervals, and has remained entirely free of abdominal pain for the past two years.

CASE 2.—J. M. is a 7-year-old white male. His birth was normal; however, his development was somewhat delayed. He did not sit up until 10 months of age, did not walk until 26 months, and began saying words at 3½ years of age. He had no specific illnesses, no operations or accidents. There was no history of lead ingestion.

When he was 4 years old, he began having severe abdominal pain, paroxysmal in nature, lasting fifteen to twenty minutes. The pain recurred on the average of one to two times a week. In each instance, the pain was followed by a short period of sleep and exhaustion.

He was admitted to the Harriet Lane Home at 5 years of age, and except for mental retardation, all examinations were negative. A routine electroencephalogram (Fig. 2), however, revealed a severely abnormal brain wave pattern with many abnormally slow high voltage waves and high voltage slow spike and wave forms.

He was discharged from the hospital without medication with instructions to return in several months for a check-up. About two weeks after discharge from the hospital, he began having frequent daily grand mal convulsions in addition to the attacks of abdominal pain. The attacks of abdominal pain occurred independently of the grand mal convulsions.

He was treated with phenobarbital without benefit and was then started on 100 mg. of Dilantin three times a day. He has been entirely free of both grand mal seizures and abdominal pain for a period of one year since starting the Dilantin.

CASE 3.—R. O. is a 10-year-old white male. Birth and childhood development were normal. The family history was negative for epilepsy or allied disorders.

He was apparently in good health until 9 years of age at which time his mother found him lying on the bathroom floor in an unconscious state. No convulsive movements were observed. The mother stated that she saw him about one-half hour before, and he appeared to be feeling well.

He was immediately taken to one of the local hospitals. Routine physical and neurological examinations revealed a comatose 9-year-old male. Examinations were otherwise essentially negative. He regained consciousness after about four and one-half hours and felt well except for a moderate degree of drowsiness which lasted for several hours.

Repeated physical and neurological examinations were negative. Laboratory tests including urine, blood chemistries, spinal fluid, x-ray of the skull, and pneumoencephalogram were all normal.

He remained in the hospital for ten days and was discharged in good condition. He was then referred to us for further investigation.

A routine electroencephalogram was done twelve days after onset of the episode of loss of consciousness. At the onset of this test, the patient had had no specific complaints. Ten minutes after the test was started, the patient suddenly began to complain of a very severe knifelike pain in the region of the umbilicus. The pain persisted for about ten minutes and then abruptly stopped. He was somewhat drowsy and confused for about fifteen minutes afterward. The electroencephalographic examination was continued throughout the entire interval of pain and for fifteen minutes thereafter.

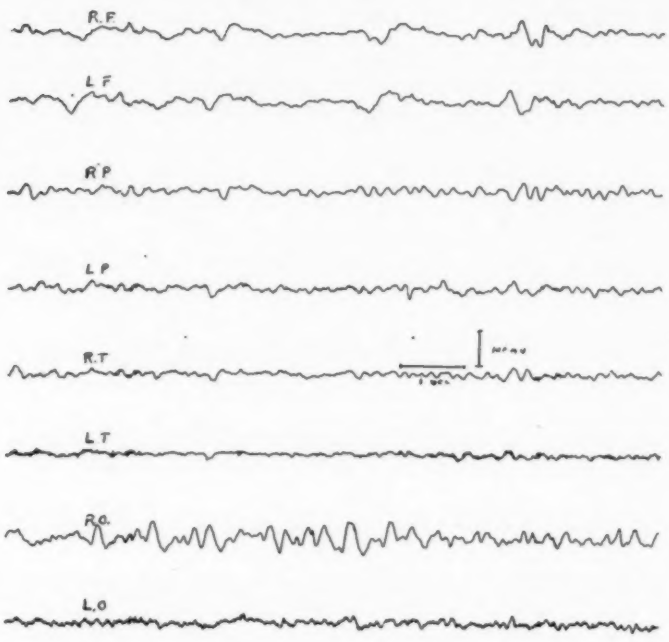

Fig. 3.—Sample of EEG of R. O. taken at onset of test shows abnormally slow high voltage waves present only in the right occipital lead. The patient was asymptomatic at this time.

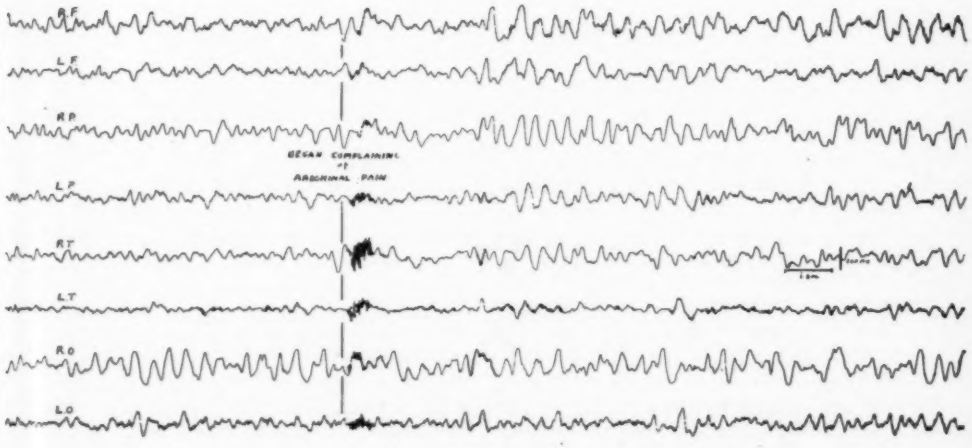

Fig. 4.—Sample of EEG of R. O. taken just at onset of abdominal pain indicated by a point marked with vertical lines on tracing shows a generalized build-up of high voltage slow waves in all leades.

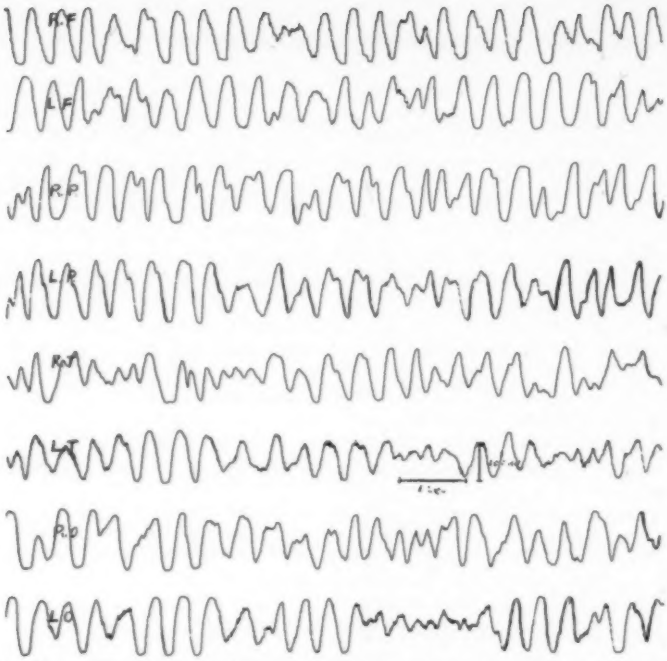

Fig. 5.—Sample of EEG of R. O. taken two minutes later while he was still having pain shows an almost constant run of very high voltage two per second waves in all leads.

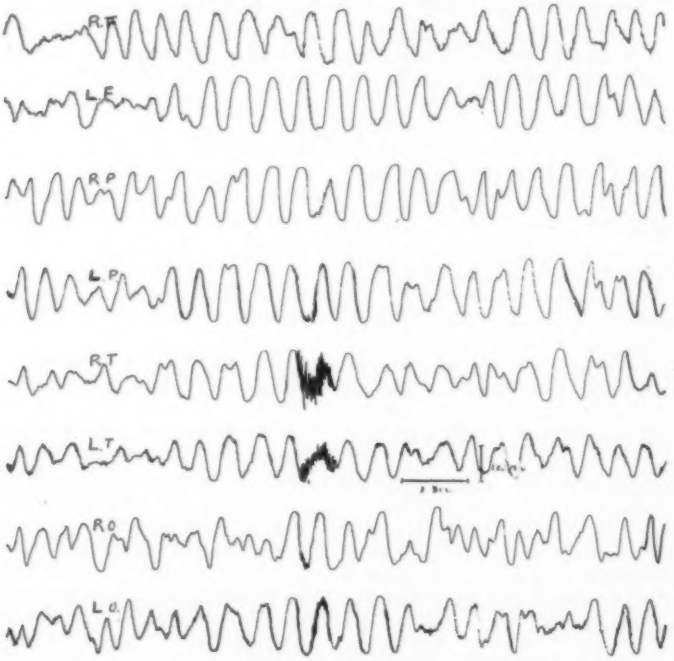

Fig. 6.—Sample of EEG of R. O. taken eight minutes later while the pain was still present shows abnormalities almost identical with those present in Fig. 5.

Serial samples of this test are shown in Figs. 3, 4, 5, 6, and 7.

He was given 100 mg. of Dilantin three times a day and has been free of abdominal pain or other manifestations of epilepsy for a period of nine months.

the pain, his stomach becomes very tense, and "he cries and cries and then vomits. He usually sleeps for several hours after the pain is over." The pains almost always occur between 5 and 7 A.M. and frequently awaken him from sleep.

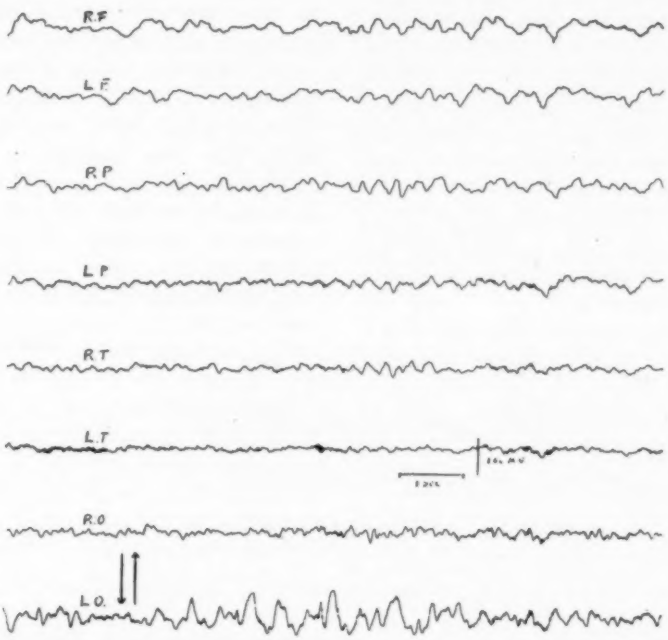

Fig. 7.—Sample of EEG of R. O. taken fifteen minutes after abdominal pain had ceased shows abnormally slow high voltage waves present only in right occipital lead similar to the abnormalities demonstrated in Fig. 3, before the onset of the abdominal pain.

CASE 4.—M. O. is a 10-year-old white male. His birth and childhood development were normal. There is no history of epilepsy or allied disorders in the family.

About two years ago, he began having "gripping pains in the stomach," which recurred about every two weeks until he was first seen by us at 8 years of age. The pains are described by the patient as follows: "They just grip me. They go off and on for about five to ten minutes. I vomit when I have these pains. It feels like somebody is grabbing and squeezing my stomach." The mother states that when he has

Physical examination at the time he was first seen by us revealed a somewhat thin, but fairly well-developed 8-year-old boy. He appeared to have at least average intelligence for his age. No gross physical abnormalities were present. Neurological examination revealed no pathological findings.

Laboratory examinations, including urinalysis, blood chemistries, x-ray of the skull, intravenous pyelogram, and gastrointestinal barium studies were normal. A routine electroencephalogram revealed an abnormal brain wave pattern with three paroxysmal bursts of spikes in all leads (Fig. 8). Two

of these bursts of spikes appeared during rest and one during hyperventilation.

He was given 32 mg. of phenobarbital four times a day. However, the pain recurred, and during the course of the subsequent six months, the phenobarbital was increased to 64 mg. four times a day and was continued for three months but without benefit. The phenobarbital was discontinued, and the patient was given 100 mg. of Dilantin three times a day. The abdominal pain recurred as before, and the Dilantin was increased to the maximum tolerance without benefit. Several months ago, he was given 5-phenyl, 3-methyl hydantoin (Nuvarone). This drug has not been used long enough to determine its anticonvulsant value.

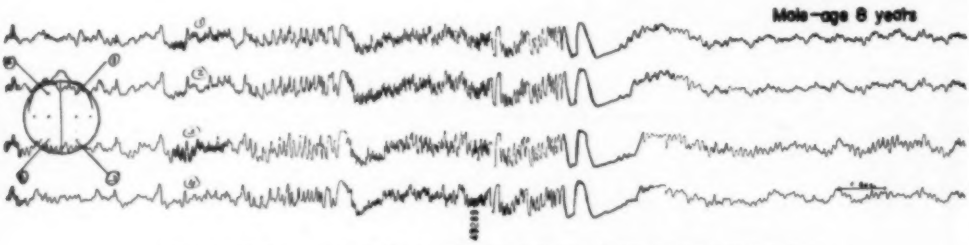

Fig. 8.—Sample of EEG of M. O. The patient was asymptomatic at this time.

DISCUSSION

The results of this study, along with those previously reported by Moore and Hoefer indicate that paroxysmal attacks of abdominal pain may be a manifestation of abnormal cerebral activity.

All of the fourteen patients studied by us presented one or more of the following features: (1) recurrent paroxysmal attacks of abdominal pain followed by postictal-like exhaustion and sleep, (2) electroencephalographic abnormalities, and (3) a favorable clinical response to Dilantin therapy.

It should be emphasized, however, that a diagnosis of so-called abdominal epilepsy may be entertained in patients who suffer with recurrent attacks of abdominal pain and yet do not present the typical triad of findings as previously mentioned.

All of the fourteen patients studied by us presented recurrent attacks of abdominal pain which was followed in each instance by a state of exhaustion and sleep. However, in Moore's and Hoefer's series, there were some patients who were classified as having abdominal epilepsy, but in whom the abdominal pain was not followed by exhaustion and sleep. It is readily conceivable that sleep or exhaustion need not necessarily be an associate of the abdominal pain, since it is generally known that many patients with overt epilepsy do not go into a state of exhaustion at the termination of their seizures.

Of the fourteen patients studied by us, ten presented abnormal electroencephalographic findings, and four had normal brain wave patterns. Hoefer reported that thirty of his thirty-one patients revealed abnormalities in the electroencephalogram.

All of the electroencephalograms performed on our patients were routine tests. It may be that if means of activation, such as sleep, photo-driving, or Metrazol were employed, a

greater number of electroencephalographic abnormalities might have been found.

The presence of a normal electroencephalogram should not necessarily eliminate the diagnosis of abdominal epilepsy in any given case if the history and therapeutic test validate such a diagnosis. It is generally known that a varying percentage of patients with definite clinical evidence of other forms of epilepsy not infrequently present normal brain wave patterns.

Probably the most important of the three criteria mentioned is the clinical response to anticonvulsant therapy, although it should be emphasized that a failure to respond to anticonvulsant medication does not disprove a diagnosis of epilepsy in any form.

Eleven of our fourteen patients have been completely relieved of their seizures with Dilantin. The remaining three patients were not favorably affected with the use of Dilantin and phenobarbital. These patients are now being treated with other anticonvulsants.

In conclusion, it should be stressed that since abdominal pain is probably one of the most common complaints which a pediatrician is called upon to interpret and may be a symptom of many disorders, each patient should be investigated very intensively before a diagnosis of abdominal epilepsy is made.

SUMMARY

1. Clinical and electroencephalographic studies on fourteen children who suffered with recurrent paroxysmal attacks of abdominal pain considered to be of cerebral origin (abdominal epilepsy) are presented.

2. All of these patients presented one or more of the following features:

a. Recurrent attacks of abdominal pain followed by postictal-like exhaustion and sleep.

b. Electroencephalographic abnormalities.

c. A favorable clinical response to Dilantin therapy.

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PRENATAL MULTIPLE IMMUNIZATION

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WHOOPING cough and diphtheria remain the two most important preventable contagious diseases of infancy. During the first two years of life, the former disease is still the cause of more deaths than measles, diphtheria, poliomyelitis, and scarlet fever combined. The easily performed Schick test and the precision of antitoxin determinations have yielded abundant data regarding diphtheria immunity, while the absence of such tests has accounted for the relative lack of authentic information about pertussis immunity in the adult and in the infant. By means of the Schick test and antibody titers we have demonstrated a decline in diphtheria immunity in the past generation.[1] This has been further evidenced by the fact that numerous outbreaks and epidemics of the disease have been reported in different parts of the world, and a progressive increase in the case rates has occurred since 1945. These cases have been almost evenly distributed between the age groups of 1 to 5 years, 5 to 10, and above 10 years.[2-10]

Mishulow and her co-workers[11] found that 15.2 per cent of children and adults who had a negative history of pertussis had protective antibodies. Their immunologic study of a group of women reveals that 31 per cent had pertussis antibodies prior to inoculation. Since these antibodies are transmitted from the pregnant mother to the baby, a small but definite proportion of babies may be born with some immunity against whooping cough. The great majority, however, have no protection against this disease.

Scadron and Cohen[12] injected a group of pregnant women at two-week intervals from the sixth to the eighth month of pregnancy with doses of pertussis vaccine totaling from 90 to 150 billion bacilli. Immunologic studies demonstrated that all developed high titers of immune bodies following such vaccination, and that these antibodies were regularly transmitted to the newborn babies in a high titer quantitatively of the same order. Other groups of investigators using different immunologic techniques obtained results which led to similar conclusions.[13, 14, 15]

Although the majority of adults have been shown to possess considerable quantities of neutralizing antibodies against the influenza virus,[16] there has been little available data comparing influenza antibody levels of mothers and their infants. Rickard and Horsfall[17] performed quantitative neutralization tests with influenza A virus and the serum of noninoculated mothers and their infants at various periods after birth. They found that during the first two months of life, infants possess antibody levels almost identical with those of their mothers. During the third and fourth months, antibody

From the Pediatric Service of the Beth Israel Hospital.

levels decreased rapidly in infant serum, and from the fourth to the sixteenth months, very few infants possessed demonstrable concentrations of antibodies against this virus. Cohen and Schneck[18] demonstrated that children under 2 years of age who were actively immunized against influenza did not respond with good antibody production.

The great susceptibility of adults and children to whooping cough, and the importance of this disease as a cause of infant mortality, the demonstrated decline in immunity to diphtheria among adults within the last generation (and a consequent decrease in newborn immunity)[13, 19] and the difficulty of immunizing children under 2 years of age against influenza if need be, suggested to us the advisability of protecting the newborn infant against these and additional diseases by the method of maternal immunization, but using multiple antigens instead of a single antigen.

METHODS

A group of unselected women patients in the pre-natal clinic of the Beth Israel Hospital, New York City, were Schick tested on admission to the clinic. Immunization procedures were carried out on these women in the last trimester of pregnancy. Schick-positive mothers were immunized against both diphtheria and whooping cough, Schick-negative mothers against whooping cough alone. Certain patients of both groups were inoculated with a single injection of influenza virus vaccine.

The injections were begun in the seventh month of pregnancy and so spaced that immunization was completed approximately six weeks before delivery. The immunizing series for pertussis and diphtheria consisted of three injections given at intervals of four weeks. For influenza immunization, one injection was given six weeks before the expected date of delivery. Blood for titration of antibodies was taken from the mother before the immunizing series was begun, and again at delivery. Cord blood, representing the fetal circulation, was also taken at delivery.

Vaccines used were of two varieties, fluid and alum precipitated. The alum-precipitated material yielded by virtue of three immunizing doses 100 to 150 flocculation units of refined diphtheria toxoid and 97 billion killed *Hemophilus pertussis* phase I bacilli, and the fluid products, 100 to 120 flocculation units of diphtheria toxoid and 120 billion killed *H. pertussis* phase I bacilli. Influenza virus vaccine used was type A and B calcium phosphate adsorbed, and contained the following strains of virus: PR8, Lee, FMI, and Weiss. This material is available commercially.*

Pertussis titrations were done by a standard agglutination method.[20] Diphtheria antitoxin titers were done by the method of Frobisher.[21] Influenza viral antibodies (PR8 and Lee strains) were titrated by the red cell agglutination inhibition reaction of Hirst.[22]

Immunized infants were returned to the Well-Baby Clinic for pediatric care and supervision. It was thus possible to follow, for several months, a number of these infants passively immunized ante partum. Blood for titration was taken at three, six, and nine months, during which time immunizations were withheld, after which the

*Parke, Davis & Company.

children were immunized in the routine manner.

RESULTS

One hundred and six pregnant women were immunized against pertussis in the last trimester of pregnancy and bloods were taken for titrations at delivery from mother and baby (cord blood). Results are shown in Table I and are grouped as follows:

1. Excellent response. A marked increase in agglutination titer and resulting levels well above those considered necessary for good immunity (1:500 or over).[23, 24]

2. Good response. Moderate or good increase in agglutination titer with resultant levels at or slightly above those considered necessary for good immunity (1:300 to 1:500).

3. Poor response. Little significant rise in agglutination titers and resultant levels below those considered to represent good immunity.

4. No response.

After exclusion of a number of cases which had been shown to be false Schick positives,[25] the results on twenty-four mothers and babies were studied at delivery. In these cases the mothers had been Schick positive, control and Moloney tests negative, and their post-Schick tests-preimmunization titers were less than 0.01 unit of circulating antitoxin. The results tabulated are as follows:

1. Excellent response. Levels above 0.1 unit of circulating antitoxin per cubic centimeter of blood.

2. Good response. Levels between 0.01 and 0.1 unit of circulating antitoxin per cubic centimeter of blood.

3. Poor response. Levels under 0.01 unit of circulating antitoxin per cubic centimeter of blood.

These results are shown in Table II.

Eighteen mothers were given a single 1 c.c. injection of influenza virus vaccine six weeks antepartum and bloods were drawn at delivery from mother and baby. The results have been organized as follows:

TABLE I. RESULTS OF MATERNAL PRENATAL IMMUNIZATION WITH PERTUSSIS VACCINE

	EXCELLENT	%	GOOD	%	POOR	%	NONE	%	TOTALS
Mother	50	47.2	38	35.8	14	13.2	4	3.8	106
Baby	50	47.2	38	35.8	14	13.2	4	3.8	106

TABLE II. RESULTS OF MATERNAL PRENATAL IMMUNIZATION WITH DIPHTHERIA TOXOID

	EXCELLENT	%	GOOD	%	POOR	%	TOTALS
Mother	13	54.2	6	25	5	20.8	24
Baby	12	50	7	29.2	5	20.8	24

TABLE III. RESULTS OF MATERNAL PRENATAL IMMUNIZATIONS WITH INFLUENZA VIRUS VACCINE

	EXCELLENT	%	GOOD	%	POOR	%	NONE	%	TOTALS
Mother	8	44.4	6	33.3	2	11.1	2	11.1	18
Baby	8	44.4	6	33.3	2	11.1	2	11.1	18

TABLE IV. DURATION OF IMMUNITY IN PASSIVELY IMMUNIZED IFANTS

	3 MONTHS		6 MONTHS		9 MONTHS	
	TESTED	IMMUNE	TESTED	IMMUNE	TESTED	IMMUNE
Diphtheria	18	11 (61.1%)	8	1 (12.5%)	3	0 (0%)
Pertussis	36	16 (44.4%)	9	0 (0%)	3	0 (0%)

1. Excellent: Fourfold or greater increase in agglutination titers in both PR8 and Lee strains and final levels well above those considered good immunity (64 or higher).[18]

2. Good: Twofold to threefold increase in agglutination titers and final levels at accepted good levels of immunity (8 to 64).

3. Poor: Twofold increase or less with resultant levels low (less than 8).

4. No response.

These results are shown in Table III.

titers. The results are shown in Table IV and Fig. 1.

All mothers who had received prenatal pertussis immunizations were queried concerning the exposure of their infants to pertussis during the first six months of life and the contraction of the disease. Only two of the sixty-six queried had been in close contact with cases of pertussis during the first six months of life, and neither had contracted the disease.

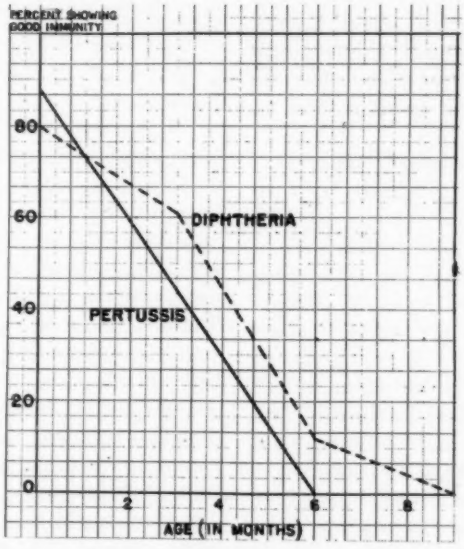

Fig. 1.—Duration of passive immunity of newborn babies.

A total of fifty-four infants whose mothers had been immunized during the last trimester of pregnancy as previously described, were bled at 3, 6, and 9 months of age, routine immunization being withheld until that time. All of the children selected had acceptable levels of immunity as demonstrated by cord blood taken at delivery. Eighteen of these were followed for diphtheria titers and thirty-six were followed for pertussis agglutination

Reactions to combined inoculations appeared to be more severe when diphtheria toxoid was included than when it was omitted. These undesirable reactions occurred most frequently with the first injection, and diminished with later injections.

With pertussis-tetanus mixtures, the great majority of reactions were mild. There was less reaction to the alum-precipitated than to the fluid preparation.

DISCUSSION

The response to the combined vaccine inoculation as measured by pertussis agglutination titers in our study was excellent. A number of investigators have presented clinical and experimental evidence for the validity of agglutination titers as an index of immunity against pertussis. [23, 24, 26, 27, 28] Almost 84 per cent of 106 immunized mothers and their newborn infants had an agglutination titer of 1:300 or over. Di Sant' Agnese,[29, 30, 31] immunizing infants one week of age, found that the number of young infants with pertussis agglutination titers of 1:400 after inoculation was never greater than 63 per cent.

Miller and associates[32] found that fluid toxoid injected initially at 4 to 8 weeks of age does not give an adequate immune response. Even alum-precipitated vaccine if begun too early (younger than 1 to 2 months of age) may not cause an adequate immune response, for age appears to be factor in serologic response to immunization. Significantly, these authors found that the serologic response of infants whose cord blood contained no agglutinins prior to immunization was not superior to that of infants with agglutinins. Hence, no depression of the immune response by passive transfer of antibodies was demonstrable. Greenberg and Fleming[33] and Fox and Snartemo[34] found that the presence of inherited antibody had some effect in depressing response to diphtheria toxoid, but was not great enough to prevent satisfactory immunization in any of their infants.

Of the infants who had excellent response at birth to pertussis immunization (1:500 or over), thirty-six were retested at 3 months of age. Of these, sixteen, or 44 per cent, still had good immunity as judged by their serum agglutination titer. Nine of these had blood drawn again at six months of age and in no case was demonstrable agglutination titer found. Three of these infants were bled again at 9 months of age and no serum agglutination was found. From this evidence we infer that the agglutination titer drops sharply until it has entirely disappeared at six months. However, it is significant that babies retain immunity up until approximately 3 months of age. This is shown graphically in Fig. 1.

The correlation between serum antitoxin titer and clinical immunity to diphtheria is much closer. Although immunity is a composite of several factors, local, cellular, tissue, and humoral immunity among others, the last two mentioned can be favorably influenced. The Schick test is a good index of humoral immunity and closely correlates with an adequate antitoxin content of the blood. However, we did not employ this test as a measure of humoral immunity to diphtheria in young infants, because there is an anergy to diphtheria toxin in the skin of the newborn infant.[35, 36] Thus a negative Schick test in the infant during the neonatal period is not consonant with immunity, as demonstrated by antitoxin titrations.

Of twenty-four Schick-positive mothers who had less than 0.01 unit of circulating antitoxin per cubic centimeter of blood, thirteen, or 54.2 per cent, had an excellent response to immunization, i.e., above 0.1 unit, and six, or 25 per cent, had a good response, i.e., a level between 0.01 and 0.1 unit. Thus about four-fifths of the mothers (hence their

newborn babies) were immune to diphtheria after immunization.

Eighteen babies who had over 0.01 unit of antitoxin per cubic centimeter at birth were retested again at 3 months of age. Of these, eleven, or 61.1 per cent, still had good immunity (titers between 0.01 and 0.1 unit per cubic centimeter). At 6 months of age, eight of these babies had blood samples drawn and only one still had adequate circulating antitoxin. Three of these infants were bled at 9 months of age and none had over 0.01 unit of circulating antitoxin. Passive immunity therefore appears to wane rapidly after 3 months of age. This is shown graphically in Fig. 1.

The response of the pregnant woman to one injection of influenza vaccine was equally gratifying. This was anticipated since the single injection acted as a booster rather than an initial stimulus, for most adults have suffered repeated exposures to infection by this virus. The increase of immunity as measured by the "fold" increase in red cell agglutination inhibition titration was, as expected, transmitted to the newborn infant. Levels were not followed after the neonatal period because other observers have shown that these fall after several months to a low level.[17] Since the work of Cohen and Schneck has shown that children below the age of 2 years do not respond to influenza vaccine with adequate antibody production even after several injections, it may be desirable at times to achieve high levels in the mothers (and their babies), so that protective titers remain for as long a period after birth as possible.

Greater efficiency in the administration of influenza vaccine would be achieved if given only during a threatened epidemic, and when the prevalent virus is antigenically related to the vaccine strains. These antigenic differences offer the major problem in influenza prophylaxis at the present time, and prophylactic vaccination in the mother with passive transmission to the infant will be accepted as a routine procedure only after means have been found to surmount this difficulty.

The optimum time for inoculation of infants born of immunized mothers would appear to be somewhere between 3 and 6 months of age. We prefer 4 months of age, because protection is present during the first twelve to sixteen weeks in a considerable proportion of babies. Furthermore, attempts to immunize these infants earlier may possibly be neutralized to some extent by the passively transferred antibodies from the mother to the offspring. It may be best to protect the young infant by passively transmitted immunity for the first three to four months, and then actively immunize him when his response to antigenic stimulus is more adequate.

It must be remembered, however, that in this study we have been dealing with a group of mothers who have been successfully immunized. When we consider that only 15 to 30 per cent of the adult general population are immune to pertussis and about 60 per cent to diphtheria, we are faced with the fact that a tremendous number of babies are born susceptible to these diseases at birth. That these observations are significant and have been borne out, one need only note the epidemics of diphtheria in newborn infants in Europe and the large number of cases of whooping cough in early infancy in this country.

There is a definite need in selected cases for prenatal immunization to safeguard the newborn infant with adequate immunity. Similarly, in influenza outbreaks, vaccination of the mothers may protect the baby during a period in which usual immunization procedures have been shown ineffective.

In previous articles, we have emphasized the frequency of diphtheria protein sensitization in the adult. This has been an important deterrent in the immunization of the adult against diphtheria. In our immunization program, we have excluded from diphtheria immunization those adults with strongly positive Moloney tests. The first diphtheria toxoid inoculation is always small in amount, serving as a testing dose. We have learned that reaction to diphtheria toxoid is decreased when the toxoid is combined with other antigens, and still further decreased when dispersed in an alum or aluminum hydroxide medium with its attendant slow absorption.

Tetanus toxoid in the form of a triple antigen (diphtheria, pertussis, tetanus) has been administered to a number of women. There was no augmentation of the local or systemic reactions, and the immunity attained has been transmitted to the baby. In our community there seemed no necessity for immunizing newborn babies against tetanus, so that this has not become our routine combined antigen for maternal prenatal immunization. It does demonstrate, however, the feasibility and facility with which immunization can be simultaneously performed against four diseases. We have contemplated the additional administration of pneumococcus polysaccharide or staphylococcus antigens, if ever there is need for immunization of the newborn infant against these disease agents. These same principles apply to other diseases for which there are effective immunizing procedures, affording the newborn infant needed protection through maternal immunization. Careful studies of the babies of hundreds of immunized mothers have revealed no ill effects from maternal immunization performed in the last trimester of pregnancy. Similarly, the immunizations had no adverse effects upon the mothers.

This suggested method does not obviate the necessity for the immunization procedures of early infancy. However, it enables us to safely postpone immunization to an age when the infant is older and better able, as has been demonstrated, to respond more quickly and with higher titers (possible because of a more mature antibody-producing mechanism). It would therefore seem to offer better over-all protection during the first year of life.

SUMMARY

1. Whooping cough and diphtheria are still the two most important preventable contagious diseases of infancy.

2. Forty to 50 per cent of mothers, and hence their offspring, are not immune to diphtheria, and only 15 to 30 per cent show immunity to pertussis.

3. In selected cases, prenatal immunization is highly desirable and sometimes necessary.

4. When women were immunized in the last trimester of pregnancy with multiple vaccines, 80 per cent or more of them responded with high titers of antibodies protecting against diphtheria, pertussis, tetanus, and influenza.

5. These protective titers were quantitatively passively transferred to the

newborn babies in whom they persisted for a period of three months or more.

6. Reactions were more severe when the combined vaccines contained diphtheria toxoid than when they did not. There was less reaction to the alum-precipitated than to the fluid preparation.

7. We have encountered no adverse effects upon either mothers or babies from inoculations given in the last trimester of pregnancy.

8. The method of prenatal multiple immunization would seem to protect the newborn baby against the threat of diphtheria and pertussis, and if need be, influenza and tetanus during the first three months of life when effective active immunity cannot be established.

9. Active immunization should follow at 3 to 4 months of age, when passive immunity has been lost, and when mechanisms for establishment of active immunity function more efficiently than at an earlier age.

We are indebted to Parke, Davis and Company for providing the immunizing and skin test materials used, and for the antibody titrations.

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STATISTICAL ANALYSIS OF 242 CASES OF MENINGOCOCCUS MENINGITIS

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THERE have been three distinct periods in the treatment of cerebrospinal fever. The first was from 1800 to the beginning of the present century. The treatment was symptomatic and supportive and the mortality rates were 70 to 90 per cent. During the second period, which followed the discovery of the etiological organism, the meningococcus, and the introduction of specific serum therapy by Flexner, the mortality rate dropped to 45 to 50 per cent. The third period began in 1936 with the advent of the chemotherapeutic drugs which further dropped the mortality figures to 0 to 15 per cent. Present efforts are directed toward making treatment more effective and the mortality rate even lower.

In the use of these drugs, however, many problems relating to the method of administration, dose, and length of treatment have arisen about which there is not yet complete unanimity of opinion. For example Sweet,[1] Dowling,[2] and some other authorities believe that frequent spinal punctures and intrathecal therapy are still necessary for the best results, while others, notably Hoyne and Brown,[3] feel that this is not required. Another point of difference concerns the use of penicillin in conjunction with sulfadiazine, which Dowling and his co-workers[2] consider advantageous, yet Hoyne[3] finds it useful only in eye complications. It is the purpose of the present report to add some data bearing on these problems.

Between 1942 and 1947, inclusive, a total of 284 cases of meningitis was admitted to the Kingston Avenue Hospital for Contagious Diseases. Of these, 242 were due to the meningococcus, and it is these which constitute the material for this study. The data were obtained from the records of the hospital and are not the results of a definite therapeutic routine since different physicians had charge of the service at different times. However, with each succeeding year, the trend seemed to be toward fewer spinal punctures.

The number of cases, deaths, and per cent fatality of all the cases (including the thirty-four cases not due to the meningococcus and the eight cases of meningococcemia) for the entire period is demonstrated in Chart I for purposes of comparison.

The seasonal incidence showed the number of admissions to be highest during the months of January, February, March, May, and August, with September having the lowest number of cases. This is similar to the findings of other observers.

A study of the occurrence and mortality according to age (Chart II)

From the Kingston Avenue Hospital.
†Deceased.

showed that the disease occurred most frequently in the age group between 1 to 5 years and 11 to 25 years, the incidence being 28.9 per cent and 28.5 per cent, respectively. The lowest was in the youngest group (0 to 1 year) and the oldest group (over 45 years). However, the mortality rate was highest in the youngest group (22.2 per cent) and this mortality decreased in each succeeding group indicating that the prognosis is least favorable in very young infants (Chart III).

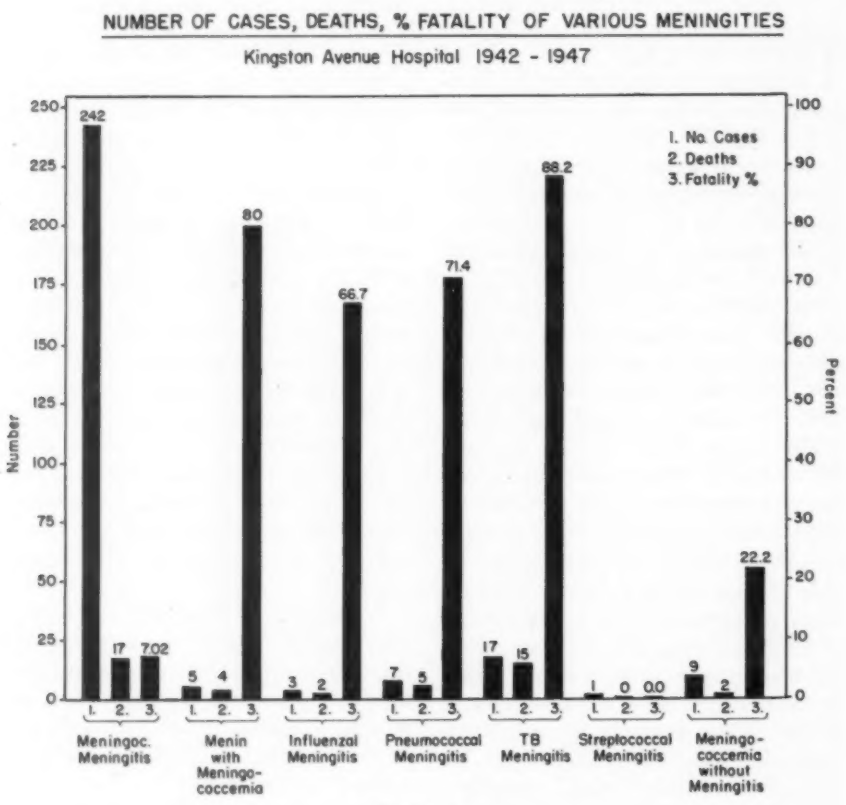

Chart I.

Of the total number of patients, 139 were males and 103 females. A detailed study of all the cases correlating age and sex for the various years showed that this proportion was similar for each year except 1942 in which there were three times as many males as females (15:5) and 1947 in which all five patients were male. The number was not great enough to be of significance except that other reports show the majority of patients to be male in approximately the same proportion. The total figures for the entire period are summarized in Table I.

The average day of illness at the time of admission varied slightly from

OCCURRENCE AND MORTALITY ACCORDING TO AGE

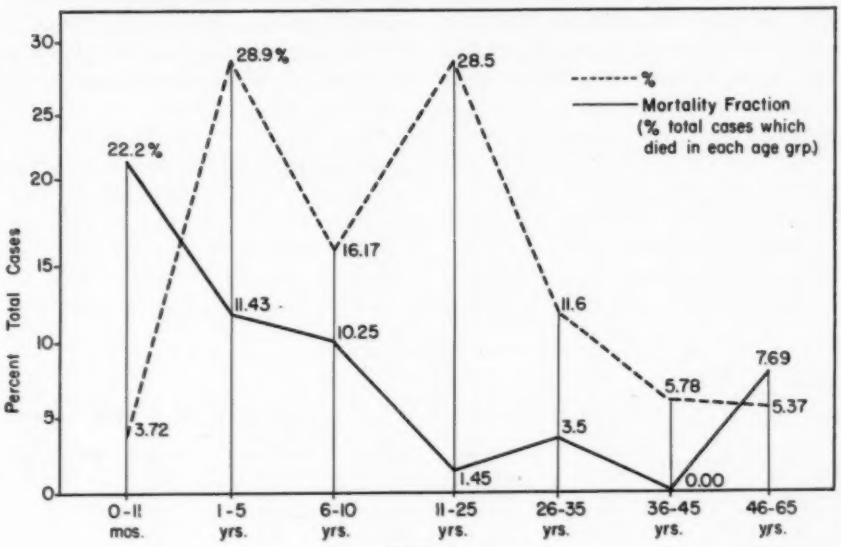

Chart II.

% FATALITY ACCORDING TO AGE

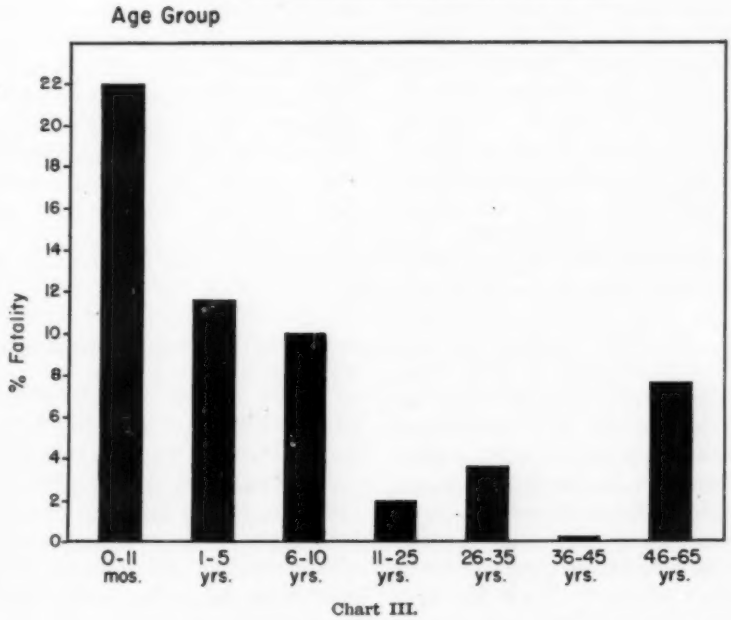

Chart III.

year to year, the exact figures being 2.47 for 1942, 1.89 for 1943, 2.23 for 1944, 2.00 for 1945, 2.24 for 1946, and 2.40 for 1947 giving an average of 2.10 for the entire series, with the variation from year to year being of little significance. In comparison with others in the literature it is quite early for these patients to be hospitalized (Hoyne's figure is 3.1 days) and it may have been a contributory factor to the low mortality figures.

An analysis of the clinical phenomena of the patients on admission to the hospital is given in Table II. The cases were divided into two groups, those over and those under 2 years of age since it has been pointed out previously[7] and by many authors[1, 8] that the diagnostic criteria are not likely to be present in the young infants.

TABLE I

		AVERAGE DAY OF ILLNESS AT TIME OF ADMISSION	
SEX		1942	2.47
Males	139	1943	1.89
Females	103	1944	2.23
RACE		1945	2.00
White	223	1946	2.24
Negro	19	1947	2.40
Other	0	Average	2.10

TABLE II

	PATIENTS OVER 2 YEARS OF AGE			PATIENTS UNDER 2 YEARS OF AGE		
SYMPTOM	TOTAL REPORTED*	POSITIVE	PER CENT	TOTAL REPORTED*	POSITIVE	PER CENT
Vomiting	188	121	64.5	26	19	73
Kernig's	178	148	83.	24	18	75
Brudzinski's	178	131	73.5	25	17	68
Nuchal rigidity	182	172	94.5	26	19	73
Opisthotonus	61	7	11.5	12	3	25
Babinski's	61	4	6.6	10	2	20
Depression of superficial reflexes	47	19	40.5	9	2	22.2
Hyperactive deep reflexes	46	10	21.8	10	1	10
Comatose (or semi-comatose)	172	37	21.5	24	7	29.1
Fever (over 100° F. on admission)	202	179	89.7	30	27	90
Petechiae	208	138	66.4	30	16	53.4
Leucocytosis (over 10,000)	144	109	75.7	17	10	58.8
Positive spinal fluid culture	181	137	75.7	26	20	77
Positive blood culture	175	50†	28.7	27	13	48.2

*According to physical examination in hospital chart by attending physician or resident physician.

†One of these was positive *Streptococcus viridans.*

CLINICAL CONDITION ON ADMISSION

Most of the patients presented the typical picture of meningitis on admission. The onset was as a rule sudden and characterized by fever, headache, vomiting, and stiffness of the neck. Twenty-six of the patients were mentally clear and 115 showed definite changes in the mental state, varying from irritability and apathy to de-

lirium and coma. In addition, almost all the patients showed the usual signs of meningeal irritation including nuchal rigidity and positive Kernig and Brudzinski signs. Ninety-two patients showed a hemorrhagic eruption. Herpes was fairly frequent. Arthralgia or arthritis was observed on admission in nine instances. The individual patients showed considerable variation in the severity of the disease, but most of them appeared critically ill on admission and some even moribund.

TABLE III. NUMBER OF SPINAL TAPS ACCORDING TO YEAR

YEAR	0	1	2	3	4	5	6	7	8	9	TOTAL	AVERAGE PER PATIENT
1942	0	3	5	5	1	4	1			1	20	3.35
1943	1	29	49	2	0	0					81	1.64
1944	0	35	23	4	2	1					65	1.63
1945	0	25	12	6	2	1					46	1.74
1946	0	18	5	1	0	1					25	1.44
1947	0	2	1	0	2	0					5	2.40
Total	1	112	95	18	7	7	1			1	242	1.79

The eight cases of meningococcus bacteremia without evidence of meningeal involvement showed the usual septic temperature and the presence of an extensive hemorrhagic or polymorphous eruption. Arthralgia was present in four instances. The spinal fluids were normal in all.

BACTERIOLOGIC DIAGNOSIS

Diagnostic lumbar punctures were performed on all of the patients with meningitis on admission. The cerebrospinal fluid showed varying degrees of turbidity. The cells were greatly increased in number with polymorphonuclears predominating. In a majority of instances the protein content was moderately or greatly increased. The sugar was either absent or markedly diminished in almost all instances although in a few cases seen early in the disease the sugar content was within the normal range.

The diagnosis was confirmed bacteriologically in all cases. Stained smears of the cerebrospinal fluid showed varying numbers of intracellular and extracellular gram-negative diplococci in 121 instances. Meningococci were grown from the fluid in 110 of the 125 cases in which cultures were made. In eighty-eight cases the organisms were found both by smear and culture. Blood cultures were made in eighty-one of the cases of meningitis and were positive in thirty-three instances. The blood culture was positive in the eight instances of meningococcemia without evidence of meningitis.

The strain of meningococcus was identified in ninety-nine of the cases of meningitis and in the eight cases of meningococcemia without meningeal involvement. The organisms were typed directly from the spinal fluid by the quellung method in twenty-eight instances. In twenty cases, the meningococci obtained from the spinal fluid cultures were agglutinated by type-specific sera. In the remaining fifty-nine instances, the type was determined by agglutinating known strains of meningococci with the serum of the patient. Of these strains, 103 were type I, one was type II, and three were type IIA.

TABLE IV. SULFA BLOOD LEVELS AND FATALITY ACCORDING TO THERAPY

THERAPY	YEAR	NO. OF CASES	AVERAGE BLOOD SULFA LEVELS	NO. OF DEATHS	PER CENT FATALITY
Sulfadiazine	1942	13	7.6	1	7.8
	1943	79	7.52	5	6.33
	1944	55	17.7	2	3.67
	1945	7	25.0	1	14.3
	1946	1	N.D.	0	0.0
	1947				
	Total	155	10.7	9	6.45
Sulfadiazine & Sulfapyridine	1942	7	5.3	1	14.3
	1943				
	1944	2	29.1	0	
	1945				
	1946				
	1947				
	Total	9	8.72	1	11.1
Sulfadiazine & Sulfathiazole	1942				
	1943	1	N.D.	0	0
	1944				
	1945	1	9.1	0	0
	1946				
	1947				
	Total	2	9.1	0	0
Sulfadiazine & Sulfanilamide	1942				
	1943	1	11.0	0	0
	1944				
	1945				
	1946				
	1947				
	Total	1	11.0	0	0
Sulfadiazine & Sulfapyridine & Sulfanilamide	1942				
	1943				
	1944	2	N.D.	0	0
	1945				
	1946				
	1947				
	Total	2		0	0
Sulfadiazine & Penicillin	1942				
	1943				
	1944	6	22.6	0	0
	1945	38	19.5	5	13.15
	1946	24	26.1	2	8.33
	1947	5	8.85	0	0
	Total	73	19.9	7	9.6

Of the entire group of 242, 112 patients received only 1 spinal puncture, ninety-five received 2, eighteen 3, seven 4, seven 5, and one each 6 and 9. The total number of spinal punctures was 434, the average being 1.79 per patient. As further indicated in Table III, the average fell from 3.35 in 1942 to a low of 1.44 in 1946, the figure of 2.40 for 1947 being based on too few cases. The general trend, however, is indicative of the fact that fewer punctures were being done throughout this period and that it seemed clear that the results dictated the continuance of such a policy of treatment.

TREATMENT

One hundred sixty-nine patients were treated with sulfonamides only and seventy-three with sulfadiazine and penicillin. In the first group, various combinations of sulfadiazine, sulfathiazole, sulfapyridine, and sulfanila-

mide were tried, although all were discarded in a short time. There were only fourteen in this group, and they were included in the sulfa-only group. The remaining 155 patients were treated with sulfadiazine alone in the years 1942 to 1944. From 1945 to 1947 more of the patients were treated with sulfadiazine and penicillin. The results of treatment are summarized in Table IV.

It should be noted that the higher blood levels in the sulfadiazine and penicillin group are due to the fact that the dosage of sulfadiazine was increased in the later years during which period most of these cases were seen. However, it has been pointed out by others that the effectiveness, clinical course, and ultimate outcome of the case are not parallel to the blood sulfa level. The results here show a definitely lower mortality for the group treated with sulfadiazine alone. This is further brought out in the year-to-year figures which incidentally show the same lack of relationship between sulfadiazine blood levels and mortality figures.

DOSAGE AND METHOD OF TREATMENT

While not all of the patients were treated identically, the method of therapy described below was employed in a majority of instances: On the first day of treatment, children under 1 year of age received from 2 to 3 Gm.; children from 1 to 3 years of age received from 3 to 4 Gm.; children above that age received from 4 to 7 Gm.; and adults from 9 to 12 Gm. One-quarter to one-third of this amount was given as the initial dose and the remainder divided and administered at intervals of four hours.

In eighty-nine instances the drug was given by vein during the first twelve to fourteen hours in five per cent solution in distilled water. In very severe cases the parenteral medication was continued for a longer period of time. In the remaining cases, the drug was administered orally from the start. It seems logical that the parenteral routes should be reserved for the severe cases and for those patients who are unable to take or retain oral medication. There is no indication for the use of the drug intrathecally. We believe that it is dangerous to make the first dose a massive one, especially when given by vein, because of the danger of renal shut-down. Similarly, it is undesirable to give large amounts of the drug simultaneously by vein and by mouth. Following the first twelve to fourteen hours, the patient is as a rule able to take medication orally.

It is essential that during the course of sulfonamide therapy the patient should receive a sufficient amount of fluid to maintain an adequate renal output, particularly when large amounts of the drug are administered intravenously. We agree with Dowling[2] in recommending the administration of at least 3,000 c.c. of fluids a day in order to insure a urinary output of 1,200 c.c. or more daily. This is of particular importance in cases of meningitis because of the danger of dehydration due to frequent vomiting early in the course of the disease.

Finland[11] and Long[12] have pointed out that sulfadiazine readily enters the cerebrospinal fluid and maintains a level of about two-thirds to four-fifths of that found in the blood. Determinations made on blood and cerebrospinal fluid in fourteen instances supported

these observations. In joint exudates the concentration of the drug more nearly approximates that of the blood.

RESULTS

As a rule, the patients showed striking clinical improvement on the second or third day of chemotherapy. In most instances the temperature dropped by crisis or by rapid lysis. While subjective improvement was apparent early, the abnormal neurological signs usually persisted for a longer period. Indeed, nuchal rigidity not infrequently lasted well into convalescence.

Following the initial response, there was usually progressive clinical improvement and the temperature remained normal. Subsequent elevations in temperature were as a rule indicative of either a drug intoxication or the development of a complication.

There is at present a great deal of uncertainty with regard to the duration of the chemotherapy and the total amount of drug required in each case. Early in this study, the administration of sulfadiazine was continued for about four to five days after the temperature had become normal. More recently, it has been felt that chemotherapy may be safely discontinued after the patient has been afebrile for twenty-four to forty-eight hours and has received a total of 15 to 20 Gm. of the drug. It is unnecessary to use more than that amount of sulfadiazine in the average case, although an occasional instance may require a larger quantity. As a matter of fact, recovery has been seen with 12 Gm. or less in sixteen instances, in four of which the patient received a total of only 7 to 8 Gm. of the drug. It is unnecessary and may even prove harmful to administer too much of the sulfonamide or to use it too long. The ill effects from overtreatment are much more frequent than is generally realized.

The question arises as to when the infection may be regarded as having come under control. We have found that with few exceptions the disease is well controlled when the patient shows a decided improvement in his mental state, has been afebrile for twenty-four to forty-eight hours, and has received a total of 15 to 20 Gm. of the drug. As a rule, it is not necessary to resort to lumbar puncture for the purpose of evaluating the progress of the case. An examination of the cerebrospinal fluid may be indicated in those instances in which the course of the disease is unclear or the cause of a persistent fever is not apparent.

In this connection, it may be of value to comment on a certain feature of the spinal fluid examination. Undue stress is often laid on the importance of the total cell count. We have often discontinued chemotherapy in the presence of a considerable pleocytosis. A rise in the sugar content of the cerebrospinal fluid and the disappearance of the organisms are the most reliable indices. However, control of the infection is not infrequently attained before the return of the sugar to normal. Incidentally, it is worthy of note that there was no relapse or recurrence of the infection in any of the patients in this series or in any of our patients treated with other sulfonamides.

The total number of deaths in the entire series of 242 cases were seventeen, a mortality of 7.02 per cent. If the deaths that occurred within twenty-four hours are omitted, the corrected mortality becomes 1.65 per cent.

TABLE V. FATALITIES ACCORDING TO AGE AND YEAR

According to Age

AGE	NO. OF CASES	24-HOUR DEATHS	DEATHS EXCLUDING 24-HR. DEATHS	TOTAL DEATHS	FATALITY PER CENT
0-11 mo.	9	2	0	2	22.2
1-5 yr.	70	6	2	8	11.43
6-10 yr.	39	3	1	4	10.25
11-25 yr.	69	1	0	1	1.45
26-35 yr.	28	1	0	1	3.57
36-45 yr.	14	0	0	0	0.00
46-65 yr.	13	0	1	1	7.69
66 plus	0	0	0	0	0.00
Total	242	13	4	17	7.02

Fatality Rate excluding 24-hour deaths 1.65%

According to Year

YEAR	CASES	DEATHS	FATALITY PER CENT	YEAR	CASES	DEATHS	FATALITY PER CENT
1942	20	2	10.0	1945	47	6	12.75
1943	81	5	6.18	1946	25	2	8.0
1944	64	2	3.12	1947	5	0	0.0

COMPLICATIONS AND THEIR THERAPY

There were relatively few complications in this series. Arthritis involving one or more joints was the most common of these. It occurred in fifteen cases. In five instances it was present on admission, and in the remaining ten cases it appeared anywhere from the third to the eighth day. Most of the involved joints showed swelling and tenderness. A suppurative arthritis was relatively uncommon and was as a rule monarticular. The development of arthritis was an important cause of either a persistent or rising temperature after the third day. The treatment of this complication consisted of immobilization of the involved joint, resumption of the sulfadiazine, and, occasionally, aspiration. All these patients recovered completely.

One patient had a bilateral otitis media on admission. Following myringotomy, the condition cleared up completely. Cystitis was observed in one case. One patient developed an extensive left femoral thrombophlebitis on the eleventh day. The condition responded promptly to sulfadiazine. There was one instance of uveitis, which was treated successfully with chemotherapy. It may be noted that before the advent of sulfonamide therapy this complication usually led to a panophthalmitis and permanent blindness. The low incidence of serious complications was quite remarkable.

TOXIC EFFECTS OF THE DRUGS

Toxic reactions referable to the sulfonamides were encountered in sixty of the patients. The most common toxic reactions encountered in this series were related to the urinary tract. Hematuria was observed in fifty-two patients, in thirty-six of whom it was microscopic and in sixteen gross. Since we have no records of daily urine examinations in every case, it is possible or even probable that the incidence of hematuria was somewhat higher. Most of the patients developed

a renal complication on the second to fourth day of chemotherapy. In one instance hematuria appeared five days after the withdrawal of chemotherapy. It may be noted also that the occurrence of these untoward reactions was not definitely attributable either to the total amount of drug used or to its level in the blood. A diminished urinary output is probably an important factor in the causation of the renal complications. Although we do not have precise information on fluid balance in our series, it is our impression that this opinion is warranted. It is of importance, therefore, to maintain a urinary output of at least 1,200 c.c. in each twenty-four-hour period.

The nature of the renal damage is at present not entirely clear. Several observers have pointed out that there are many types of renal lesions, namely, a mechanical blockage of the urinary passages by concretions of crystals, and toxic effects on the tubular epithelium and glomeruli.

Most of our renal reactions cleared up rapidly following the early institution of conservative measures. These included the immediate withdrawal of the drug and forcing of fluid. In two instances, obstruction of the urinary tract resulting from the deposition of sulfadiazine crystals was relieved promptly by ureteral catheterization and pelvic lavage. In most of our patients the hematuria cleared up within forty-eight hours after the drug was stopped. The finding of even a few red blood cells in the urine may be regarded as a danger signal and as an indication for the withdrawal of the sulfadiazine. This is a very important precautionary measure and indicates the need for daily urine examinations. It is safe to resume the chemotherapy, if necessary, twelve to twenty-four hours after the urine has cleared, as was demonstrated in four of our cases. There is growing clinical evidence that alkalinization of the urine increases the solubility of the drug and decreases the likelihood of renal reactions, particularly of the obstructive type. However, the presence of crystals in the voided urine should not be considered an indication for stopping chemotherapy provided the urinary output is good.

The second most important toxic effect that we have encountered in our series was drug fever, which was noted fifteen times. In eight patients it was the only complication, while in seven it occurred in conjunction with some other form of intoxication. When the drug fever appeared alone, its onset was usually in the course of treatment. It is probable that this complication was even more frequent than is indicated by our figures, since its recognition is often difficult. Contrary to the general belief that this reaction occurs toward the end of the first week, we have usually noted its appearance as early as twenty-four to forty-eight hours after the beginning of chemotherapy. This early drug fever was suspected when, after the initial defervesence, followed by a short period of clinical improvement varying from a few hours to one or two days, the patient became subjectively worse and the temperature rose. The ascent of the temperature was usually steplike or irregular in manner. Withdrawal of the drug resulted in a fall of the temperature by crisis in all but one instance. In this exceptional case the defervescence was by lysis lasting four to five days. There was one instance in which the fever developed on the

day the drug was discontinued and dropped by crisis two days later.

When it is difficult to decide whether the secondary rise in temperature is the result of drug intoxication or the persistence of the infection, assistance may be obtained from lumbar puncture. If the cerebrospinal fluid shows improvement as evidenced by a drop in the cell count, an increase in the sugar, and an absence of organisms, one may safely withdraw the drug. On the other hand, if the spinal fluid findings indicate a still active infection, it is necessary to continue the chemotherapy.

Although there is a growing body of evidence indicating that all members of the sulfonamide group have a toxic effect on the nervous system, the subject has not received sufficient attention. A number of investigators have noted the development of injury to the nervous system of animals fed a variety of sulfonamides. Clinical reports indicate that these drugs produce widely varied types of toxic nervous reactions. These include the peripheral neuropathies, deafness, optic neuritis, blindness and other visual disturbances, encephalomyelitis, encephalopathy with or without convulsions, mental confusion, psychoses, and disturbances of speech. It has also been suggested that sulfonamides appear more neurotoxic in the presence of pre-existing disease of the nervous system.

A variety of blood dyscrasias, including agranulocytosis, thrombocytopenia purpura and hemolytic anemia, have been reported following sulfadiazine treatment. We have not encountered any of these serious blood reactions. Moderate drops in the leucocyte count from high or normal figures to below normal occurred in three cases (from 22,000 to 4,320; 20,950 to 4,800; 9,000 to 4,800). These did not constitute an indication for withdrawal of the drug. There were three patients with leucocyte counts below 6,000 whose counts rose during therapy. In one of these, the number of leucocytes rose from 1,100 before treatment to 12,000 on the second day of treatment. It is evident that the presence of an initial leucopenia is not a contraindication to the use of chemotherapy.

A skin eruption was noted in ten patients. This was of the morbilliform type and was associated in each instance with a slight rise in temperature from 100° to 101.8° F. In one case the rash appeared on the second day of therapy, and in the other two on the fourth day. The concentration of the drug in the blood was relatively low in all of the cases. It would seem that the development of this complication is not dependent on either the total amount of the drug administered or its concentration in the blood. It should be noted that in each instance the rash disappeared twenty-four to forty-eight hours after withdrawal of the drug. There was little difference between the rash in the penicillin-sulfa and the sulfa-only group.

We have discussed the toxic reactions at length because a knowledge of these is of basic therapeutic importance. The intelligent planning of dosage and the proper evaluation of the patient's response to chemotherapy in measure depend upon the physician's understanding of the untoward effects. Constant vigilance and the prompt institution of remedial measures with the earliest appearance of toxic signs will insure the safe use of this very valuable drug.

SUMMARY

A statistical analysis of 242 cases of meningococcus meningitis observed over a five-year period is presented. Thirty-four cases of other types and eight cases of meningococcemia seen during this period are compared statistically. Drug therapy including types, methods of administration, and complications are discussed at length. The conclusion from this study is that sulfadiazine alone gives the optimal results and that spinal puncture should be reserved for diagnostic purposes only.

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HEMOLYTIC DISEASE OF THE NEWBORN IN DIZYGOTIC TWINS: AN INTERESTING FAMILY HISTORY

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DURING the past decade there have been many noteworthy advances in the knowledge of the pathogenesis and therapy of hemolytic disease of the newborn. The Rh factor and other blood grouping incompatibilities have been firmly established as the main causative agents in this condition. In recent years the Rh factor itself has been broken down into subgroups so that a more specific fraction can be identified as the cause. Blocking and saline antibodies have also been described, which in earlier studies were not considered, and, therefore, prevented a detailed study of the cases reported.

The number of cases of hemolytic disease of the newborn reported in the literature has been increasing each year. However, there have been relatively few cases reported in which twins were involved.[1, 2, 3, 4, 5, 6, 7, 8, 9, 10]

It is, therefore, felt that the case to be presented will prove to be of interest.

CASE REPORTS

The present report describes hemolytic disease of the newborn in dizygotic twins in a family in which they were the eleventh and twelfth full-term births. The family history, which is summarized in Table I, suggests that there were at least five infant fatalities previously in which the cause of death in all probability could be attributed to hemolytic disease of the newborn.

At birth, the twins, who were born forty miles from Louisville, appeared normal, but because of the family history and the initial blood studies suggesting hemolytic disease of the newborn, the infants were transferred to the Children's Hospital. They arrived four hours after delivery.

CASE 1.—The initial physical examination on the first twin G.O. revealed the following:

Temperature 97.2° F., pulse 130, respirations 26, and weight 7 pounds, 6 ounces. The general appearance was that of a well-developed newborn male in no acute distress. The cry was good. There were no signs of icterus or edema, nor was there any evidence of a rash. The lungs and heart were negative. The liver and spleen were not palpable. The deep reflexes and the Moro were intact.

Initial blood studies on admission revealed twin G.O. to be type A, Rh+ (87 per cent). The Coombs test was strongly positive. There were 17.5 Gm. of hemoglobin, 4.34 million red blood cells, 17,650 white blood cells, and 1,589 nucleated red blood cells per cubic millimeter.

Three hours following admission twin G.O. was observed to be slightly icteric. This persisted all that day and by the following morning it had progressed to a severe degree. In the meantime his blood values were checked at regular intervals. His red blood count and hemoglobin maintained levels which were not considered alarming.

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The nucleated red blood cells, after an initial rise, gradually disappeared and none were seen after twenty-four hours of life. His liver and spleen were not enlarged to palpation. On the basis of these findings, it was decided that exsanguination was not indicated. A formula of 1:2 evaporated milk and water was started, which he frequently refused. If taken, he would vomit lieved with oxygen. Later in the afternoon he vomited about 45 ml. of formula which was followed immediately by cyanosis, sternal retraction, and a recurrence of irregular respirations. It was thought that he had aspirated some of the formula because of the numerous râles throughout the chest and impaired breath sounds. The stomach was emptied by aspiration with a

TABLE I. SUMMARY OF THE HISTORY OF THE FAMILY OF TWINS G. O. AND J. O. SHOWING THE OBSTETRICAL HISTORY WITH BLOOD TYPES OF THE LIVING MEMBERS

MEMBERS		DATE OF BIRTH	OUTCOME	BLOOD TYPE A, B, O	Rh	REMARKS
Mother*		—	—	A	cde	Anti-Rh agglutination 1.2 Saline (6-9-50) 1.8 Albumin
Father		—	—	A	cDE	
Paternal Grandfather		—	—	A	cDE	
Child No.	*Sex*					
1	M	1934	Died (10-15 min.)	–	–	Trauma at birth
2	M	1936	Died (48 hr.)	–	–	Yellow, anemic
3	F	1939	Living	A	cDE	
4	M	1940	Living	A	cDE	
5	F	1941	Died (24-48 hr.)	–	–	Yellow, anemic
6	F	1943	Living	A	cDE	
7	M	1944	Died	–	–	Stillbirth
8	M	1945	Died	–	–	Stillbirth
9	F	1947	Died	–	–	Yellow, anemic
10	M	1948	Living	A	cDE	
11	(G. O.)	1950	Died (5 days)	A	(POS. 87%)	Hemolytic disease of newborn
12	(J. O.)	1950	Living	A	cDE	

*The mother reports that during the period covered in this history, she had ten or twelve abortions, all at about three months' gestation.

TABLE II. HEMATOLOGICAL FINDINGS ON TWIN G. O.

DATE	TIME	HGB.	RBC	NRBC	WBC	SEGS.	STABS	JUV.	EOS.	BAS.	LYM.
6- 9-50*	8 A.M.	18.8	6.1	852	7,100	42	–	6	2	0	50
6- 9-50	1 P.M.	17.5	4.34	1,589	17,650	73	0	0	0	0	26
6- 9-50	4 P.M.	17.5	4.63	1,670	18,550	79	0	0	0	0	21
6- 9-50	7 P.M.	12.5	4.70	648	21,600	72	0	0	0	0	28
6- 9-50	10 P.M.	16.5	5.15	608	20,250	72	5	6	0	0	17
6-10-50	8 A.M.	17.5	5.88	1	–	74	3	0	1	0	22
6-10-50	7 P.M.	17.0	5.38	0	15,000	82	0	0	4	1	13
6-11-50	11 A.M.	18.0	5.20	0	8,900	79	0	0	2	0	19
6-12-50†	11 A.M.	18.3	5.02	0	10,800	81	0	0	2	0	17

*Results reported from hospital at which birth took place.
†Patient died June 13, 1950.

small amounts of that ingested. During the third hospital day his condition remained clinically the same. There was no cyanosis, retraction, or difficulty in breathing up to this time. However, about noon on the fourth day, the patient began having irregular, jerky respirations, and on one occasion turned cyanotic. This was resyringe. Shortly after this procedure he was bronchoscoped. There was a minimal amount of formula suctioned from the bronchial tree. This failed to improve his condition. Cyanosis, retraction, and lethargy continued despite the continued use of oxygen. The patient expired at 6:00 A.M. on the fifth hospital day.

Table II records the hematological findings on twin G.O. during his hospitalization.

A post-mortem examination was performed five hours after death. Grossly, the findings of importance on twin G.O. were generalized icterus, but no edema, patchy hemorrhages in the lungs, and kernicterus of the brain. The liver weighed 140 grams and was a dark purplish-blue in color. A cut section revealed rather severe hyperemia. The spleen weighed 15 grams. Each kidney weighed 20 grams. The pyramids of both kidneys were very dark, and the cortex and medulla were poorly differentiated. The brain appeared normal, except for a small ecchymosis on the lateral aspect of the right occipital lobe approximately 1 x 1½ cm. The brain was sectioned immediately on removal and kernicterus was found throughout. After fixation each flocculus was stained with greenish-yellow pigment. Sections revealed rather marked yellowish-green staining, described as characteristic of kernicterus. This was found particularly in the following structures: the body of the caudate nucleus, the putamen, the hypothalamic region, both mammillary bodies, Ammon's horn, the thalamus, the entire floor of the fourth ventricle, the inferior olive, the flocculi, and the dentate nucleus.

Microscopically, there was hyperemia in the liver, lungs, spleen, ileum, and adrenal glands. Areas of extramedullary hematopoiesis were found in the liver, spleen, kidneys, thymus, and lymph nodes. The lungs were described as showing intra-alveolar hemorrhage. The brain revealed focal nuclear degeneration and gliosis, but many nuclei were not involved. Some pigment was seen microscopically.

In the gastrointestinal tract chromatin was seen in the lamina of glands, and in some of the interstitial tissues of the lamina propria. As the epithelium was mostly intact, this may have been from infiltrated polymorphonuclear cells rather than epithelial cells. The cells of the submucosa were mostly mononuclear with a few eosinophiles. There was no ulceration of the mucosa.

At the tips of the pyramids in the kidneys there were focal areas of necrotic nuclear debris, some of which may have originated from infiltrated polymorphonuclear cells, but appeared to be mainly firm tubular cells. Some yellowish pigment was found in these areas.

CASE 2.—On admission the physical examination on the second twin J.O. revealed the following:

Temperature 97° F., pulse 130, respirations 28, and weight 5 pounds, 10½ ounces. The general appearance was that of a well-developed newborn male in no acute distress. There was a slight degree of icterus of the skin, but no petechiae, ecchymosis, or rash were noted. The sclerae were icteric. There was no lymphadenopathy. The spleen was not palpable, but the liver edge was felt 1 cm. below the lower costal margin. The deep reflexes and the Moro were intact.

Initial blood studies at this hospital revealed twin J.O. to be group A, Rh+ (87 per cent). He had a strongly positive direct Coombs test. There were 13.5 Gm. of hemoglobin, 3.52 million red blood cells, 25,600 white blood cells, with 6,656 nucleated red blood cells per cubic millimeter.

The family history suggesting previous deaths due to hemolytic disease of the newborn, the marked drop in hemoglobin and red cell count, and the marked rise in nucleated red blood cells (Table III), together with the infant's clinical appearance, influenced the decision to perform an exchange transfusion. This procedure was begun six and one-half hours after birth, using a plastic catheter in the umbilical vein. The technique consisted of alternately withdrawing and injecting 10 ml. samples of Group A, Rh– female blood. The total amount of whole blood infused was 520 ml., and 485 ml. were withdrawn. At the conclusion of the procedure, 5 ml. of 10 per cent calcium gluconate were injected through the vein slowly over a five-

minute period. The child was returned to the ward in fair condition. His progress in the hospital was uneventful, and he was discharged on the tenth hospital day. Table III records the hematological findings on twin J.O. during his hospitalization.

twenty-four hours. None were seen on subsequent determinations. The initial findings in this patient may be contrasted with those shown in Table III on twin J.O. On twin J.O. the drop in hemoglobin and red blood count was

TABLE III. HEMATOLOGICAL FINDINGS ON TWIN J. O.

DATE	TIME	HGB.	RBC	NRBC‡	WBC	SEGS.	JUV.	EOS.	BAS.	LYM.	MON.
6- 9-50*	8 A.M.	17.8	5.7	1418	10,130	52	5	0	0	44	4
6- 9-50	1 P.M.	13.5	3.52	6656	25,600	75	0	1	0	24	0
6- 9-50†	7 P.M.	10.0	3.75	1120	16,000	77	0	0	0	23	0
6-10-50	8 A.M.	12.0	4.2	4§	–	82	1	2	0	15	0
6-10-50	7 P.M.	11.0	3.19	114	11,400	84	0	4	1	11	0
6-11-50	10 A.M.	11.5	3.07	0	12,250	74	0	13	0	13	0
6-12-50	10 A.M.	12.2	3.7	0	7,700	65	1	9	0	23	2
6-13-50	10 A.M.	11.6	3.86	0	10,000	47	0	13	0	40	0
6-14-50	10 A.M.	11.6	3.94	0	13,600	41	0	12	0	47	0
6-15-50	10 A.M.	11.6	3.56	–	–	–	–	–	–	–	–
6-16-50	10 A.M.	11.5	3.29	–	–	–	–	–	–	–	–
6-17-50	10 A.M.	11.5	3.46	–	–	–	–	–	–	–	–

*Results reported from hospital at which birth took place.
†Patient received replacement transfusion just before these determinations were made.
‡Number per cubic millimeter of blood.
§Number per 100 WBC (no total WBC was recorded for this determination).

He was readmitted six days later for a checkup and at this time he had 9.0 Gm. of hemoglobin and 2.9 million red blood cells. Two 60 ml. whole blood transfusions elevated these values to 15.0 Gm. of hemoglobin and 4.98 million red blood cells. The patient was discharged on the fourth hospital day. A six-month follow-up revealed his condition to be satisfactory without any signs of kernicterus.

DISCUSSION

Table II reveals that during the period covered (four days of life) no serious drop in hemoglobin in the case of twin G.O. was observed. The determination at 7 P.M. on June 9, 1950, was not made by one of the regular technicians and may represent a variation in reading. The red blood cells, after an initial moderate drop during the first four hours of life, showed a tendency to increase until death. The nucleated red blood cells, after almost doubling during the first eight hours, decreased and were absent after

much greater during the first four hours. This was accompanied by an almost fivefold increase in nucleated red blood cells. Twin G.O.'s nucleated red blood count increased by less than twofold in a similar time.

The white blood cell count on twin G.O. showed a marked rise during the first four hours of life with a relatively large increase in neutrophiles. This situation persisted throughout the first two days, after which the total count decreased but the relative number of neutrophiles remained high.

Twin J.O., as can be seen in Table III, had a marked drop in hemoglobin (17.5 to 13.5 Gm.), and red blood cells (5.7 to 3.52 million) during the first four hours of life. During this period the nucleated red blood cells increased from 1,418 per cubic millimeter of blood to 6,656 per cubic millimeter. Just following the replacement transfusion, the hemoglobin was 10 Gm.; there were 4.2 million red blood cells

and the nucleated red blood cells were 1120 per cubic millimeter of blood. During the next twenty-four hours the nucleated red blood cells dropped to 114 per cubic millimeter, and none were observed on any further counts. Hemoglobin and red blood count values maintained constant levels through the period of hospitalization after exsanguination.

White blood cell counts on twin J.O. revealed an initial marked rise during the first four hours of life. There was a fall after exsanguination and thereafter a high normal value was maintained. There was a relative increase in neutrophiles which persisted from the fourth hour until the fourth day of life. An eosinophilia, beginning in the second day of life, persisted to the fifth day.

It is interesting to note that, although exposure of twins J.O. and G.O. to Rh antibody was identical insofar as the mother's antibody titer and period of time exposed is concerned, the early clinical and laboratory findings indicated a considerable difference in the type of disease which was manifest. This same observation has been made by others.[4, 6, 9] From this, it appears that no prediction as to the type of manifestation of the disease can be made on grounds of the type of exposure.

Blood types on the various members of the immediate family and the paternal grandfather, as can be seen in Table I, revealed, that with the exception of the mother, all were group A, cDE. The mother was group A, cde. It was not possible to determine definitely that the father was homozygous for the D and E factors, but the evidence would seem to indicate that such is the case. At least six of the seven deceased children died with symptoms suggestive of hemolytic disease of the newborn, and all of the living children were found to have the same Rh blood type as the father. It is of interest to note in the family history that the surviving children were not the first born, there being two deaths before a survival was recorded. The death of the first child was possibly due to injury at birth, but the second had a history suggestive of hemolytic disease of the newborn. Four of the next eight children survived. One of the four survivors has a hemiplegia of the spastic type. Thus, it can be seen that great variation has occurred in this family in the effects noted from Rh incompatibility. Four have apparently been little affected, and seven severely affected with six deaths quite probably attributable to Rh incompatibility. The seventh seriously affected child was twin J.O. who survived after a replacement transfusion.

SUMMARY

1. Cases of hemolytic disease of the newborn in dizygotic twins are presented.

2. One of the twins, J.O., was treated by means of an exsanguination procedure and survived. The other twin, G.O., died suddenly on the fifth hospital day following conservative therapy.

3. In this family there were twelve full-term births. Five children are now living, while six of them died with signs consistent with hemolytic disease of the newborn. The death of the first child was probably due to trauma at birth.

4. The deaths recorded in this family were not consecutive, even though all surviving children are Rh+ with the same blood grouping as the father.

The authors wish to express their appreciation to Mr. O. M. Alton, Chief Technician, Norton Memorial Infirmary, Louisville, Ky., for determining Rh types of the various members of the family herein reported.

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SALMONELLA INFECTIONS OF THE NEWBORN INFANT

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INTRODUCTION

THE present report describes two outbreaks of Salmonella infection in the newborn infant, one due to *S. oranienburg* and the other due to *S. bareilly*. An analysis of the epidemiology, symptomatology, and pathology is presented. Measures are suggested for the management and prevention of such epidemics.

EPIDEMIOLOGY

All cases occurred in the newborn nursery, which has a capacity of thirty-five bassinets. It is a large room with the usual facilities and adjacent utility rooms, but without cubicles for the individual bassinets. Graduate nurses, student nurses, and nurses' aides care for the infants.

The first outbreak occurred in October, 1949. On the first day, two babies (Cases 1 and 2) had loose stools. By the following day, four more babies had developed symptoms, and a 3-room system was set up for precautionary isolation. Room A was for sick babies, Room B for contacts, and Room C for unexposed, newly delivered infants. A few hours later, the hospital was closed for obstetrical cases and Room C was no longer necessary. If infants in Room B developed symptoms, they were transferred to Room A.

In spite of precautions, the epidemic continued to spread until eighteen of the originally exposed thirty-four infants showed evidence of Salmonella infection. In three cases the infection was fatal on the fourth day.

Stool cultures were performed on all babies, on the mothers, and on all personnel in contact with the obstetrical wards—doctors, nurses, nurses' aides, dieticians, maids, and maintenance workers who had worked in the nursery. Cultures were also taken at autopsy from the gastric and intestinal contents of the fatal cases as well as from heart blood, spleen, pleural and peritoneal fluid.

A Salmonella of Group C_1 (later identified as *S. oranienburg* by the Salmonella Center of the U. S. Department of Agriculture in Lexington, Ky.) was found in the stools of all affected babies, and in the intestinal contents of the three fatal cases.

Table I shows the time relationship of the appearance of positive stool cultures; Table II summarizes the results of the stool examinations in contacts.

Simultaneously, a bacteriological investigation was carried out on instruments, utensils, and food. The preparation of milk formulas was followed step by step, from its preparation through sterilization and storage to the heating prior to consumption.

With one exception, no bacteria were found in food, on instruments, or on utensils. The exception was the bottle warmer used for the reheating of the milk bottles. It was a water bath with thermostatic control, kept at 37° C. *S. oranienburg* was found in the water.

Further investigation showed that the thermostat had been out of order a few days prior to the outbreak and

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that an electrician had been called to the hospital to repair it. Stool culture of the electrician was positive for *S. oranienburg*. He remembered having had a short attack of enteritis at the time of his work at the hospital.

Table I

CASE	DAYS								
	-3	-2	-1	1	2	3	4	5	6
1	B					0	+	+	+
2	B				0	+	+	+	+
3	B					+	Exp.		
4	B				0	+	Exp.		
5		B		+	+	+	+	+	+
6		B				+	Exp.		
7			B	0		+	+	+	+
8			B			+	+	+	+
9				B		0	+	+	+
10				B		0	+	+	+
11				B	0	+	+	+	+
12				B	0	+	+	+	+
13				B	0	+	+	+	+
14				B		0	+	+	+
15					B	0	+	+	+
16					B	0	+	+	+
17						0	+	+	+
18						0	+	+	+
19						+	+		

B—Born.
Exp.—Expired.
0—Negative culture.
+—Positive culture.

Table II

Negative cultures	173
S. paratyphi, Group A	3
S. schottmülleri, Group B	2
S. typhosa, Group D	1
S. enteritidis, Group E	1
Group C_1	0
Group C_2	0

Second Outbreak.—Mrs. M. was admitted in early labor in April, 1950, and was delivered three days later. On this day the baby was handled by the mother. On the first post-partum day Mrs. M. had an attack of enteritis characterized by several loose stools and a rise in temperature to 104° F.

Her child had several loose stools on the evening of the third day. All precautions, such as isolation and the closing of the obstetrical and nursery service, were taken immediately, but seven additional infants developed diarrhea on the fifth and sixth days. The disease was mild, and all babies recovered quickly. From the stools of Mrs. M. and of the sick babies a Salmonella of Group C_1 was isolated which was identified later as *S. bareilly* by the Salmonella Center of the U. S. Department of Agriculture in Lexington, Ky.

In a thorough investigation of personnel, of instruments and utensils in the nursery and of the dietary department, no Salmonella nor other pathogens were found.

Bacteriology.—Infants' stool specimens were inoculated directly onto Salmonella-Shigella agar, bismuth sulfite agar, and Endo agar. After overnight incubation, suspensions of nonlactose-fermenting colonies were tested with polyvalent anti-Salmonella serum. Cultures which gave a positive agglutination were tentatively classified as Salmonella until detailed subculturing could be done. Almost without exception the positive stool cultures on the infants yielded a pure culture of the organism at the outset and a mixed

flora was not obtained until shortly before abatement of symptoms was noted clinically. Specimens from adults were incubated overnight in tetrathionate broth, then inoculated on Salmonella-Shigella agar, bismuth sulfite agar, and Endo agar. Nonlactose-fermenting colonies were treated in the same manner as previously described. All serologically positive cultures were subcultured on differential media and classified according to reaction. The causative organism in both outbreaks was a motile, gram-negative bacillus which did not ferment lactose, produced acid and gas in dextrose and maltose, was indol-negative and hydrogen sulfide-positive. Strongly positive agglutination reactions were obtained with Group C_1 serum. The final serological classification with flagellar antigens was done at the National Salmonella Center at Lexington, Ky.

CLINICAL FINDINGS

The main symptoms in the diseased infants were diarrhea, vomiting, leucocytosis, shock, and acidosis. Fever occurred only in a few, while subnormal temperatures were more frequent. The onset was gradual rather than abrupt. The chief clinical signs in both outbreaks are listed in Table III.

TABLE III. CHIEF CLINICAL SIGNS IN TWO OUTBREAKS OF SALMONELLA INFECTION

SIGNS	S. ORANIENBURG (18 CASES)	S. BAREILLY (8 CASES)
Vomiting	11 (including all 3 fatal cases)	1
Severe diarrhea	2	7
Loose stools	10	0
Leucocytosis	10	0
Shock (low temp.)	9	2
Acidosis	7	3
Azotemia	4 (all with acidosis)	3 (2 with acidosis)
Anuria	3 (all fatal)	0
Fever	4	0

The patients in Cases 3, 4, and 6, which were recognized on the second day of the *S. oranienburg* epidemic, developed anuria, shock, and acidosis the night of the third day. All three infants died during the fourth day.

TREATMENT

A standard regimen of treatment was instituted until vomiting had stopped and stools had improved. Nothing was given by mouth; while fluid and electrolyte requirements were met by intravenous route or by hypodermoclysis aided by hyaluronidase.

Limited amounts of 10 per cent glucose were administered intravenously because it was felt, early in the first outbreak, that the anuria in the fatal cases was of "lower nephron" origin. Acidosis was corrected by one-sixth molar lactate, sodium lactate-Ringer's solution, and Butler's solution. Each infant was given vitamin K prophylactically after five days, as suggested by Abramson.[2] Complete blood counts, blood carbon dioxide combining power, and blood nonprotein nitrogen determinations guided the treatment.

Aureomycin was used in the treatment of these patients in doses of 25 mg. per kilogram, since it inhibited growth of the organism in vitro. Clinically, however, no effect could be demonstrated on the disappearance of Salmonella from the stools in the *S. oranienburg* outbreak. In the *S. bareilly* outbreak, negative stool cultures were obtained within two to four days after aureomycin was started in all but one infant who took more than ten days to recover.

There is the possibility that the use of aureomycin might have been effec-

tive in the *S. oranienburg* outbreak in the prevention of septicemia, meningitis, or joint infections as described by Craig,[8] Almaden and Wahlen,[4] and others.[1, 14, 22]

The first six infants who developed diarrhea in the *S. oranienburg* outbreak were treated with 500 mg. of Chloromycetin every six hours on the third day; contacts were given 250 mg. twice daily. Three of the infants developed anuria, shock, and acidosis the same night. Chloromycetin was discontinued after less than twenty-four hours, because of the possible implication of drug toxicity. It did not seem to have been effective against *S. oranienburg* in this short period. In vitro studies showed the organism to be resistant to the drug. In the *S. bareilly* outbreak it was not used.

Sulfaguanidine and Sulfasuxidine were not effective in Salmonella infections, and streptomycin, although credited with success in the case of one carrier by Swiller, Swiller, and Traub,[21] was found inadequate by Seligmann and associates.[19] We did not use any of these drugs.

In one case we may have produced edema by the use of desoxycorticosterone acetate. This infant never received enough salt to produce edema. No relation was found between the administration of desoxycorticosterone acetate and acidosis or retention of nitrogen.

PATHOLOGY

The three fatal cases (Cases 3, 4, 6) showed characteristic and almost identical lesions, varying from case to case only in degree.

The stomach and intestines were markedly distended. The mucosa from the prepyloric portion of the stomach to the upper ileum was congested and covered with blood-tinged mucus. Microscopically, there was necrosis of the superficial layers of the mucosa and congestion of the submucosa, with little or no infiltration with inflammatory cells. Petechial hemorrhages and prominence of lymphatic follicles, described as characteristic by Felsen and associates,[10] were not found.

The heart was dilated in all cases. Microscopically, interstitial edema and a varying degree of myocardial degeneration were seen.

Severe passive congestion was found in all viscera. In Case 4, in which the lesion was most pronounced, red cells were densely packed in the venules and capillaries of the kidneys and in the sinusoids of the liver; this gave the impression of vascular stasis. On the other hand, many hepatic sinusoids and renal glomerular tufts appeared empty, as if under the effect of vascular spasm.

Visceral degenerative lesions were found mainly in liver, kidney, and adrenals. In the liver they were accompanied by edema with prominent spaces of Dissche, and they varied from moderate parenchymatous and fatty degeneration to scattered foci of necrosis. In Case 4, in which the lesions were most severe, they were accompanied by phagocytosis of dark-staining granular material in the Kupffer cells.

Parenchymatous degeneration of the renal tubules was most marked in the proximal convoluted tubules and in the descending loop of Henle; again, it was most severe in Case 4.

The adrenals showed extensive vacuolization of the cortical cells, particularly in the zona fasciculata, with fusion of cells and the "tubular degeneration" common in severe infections.

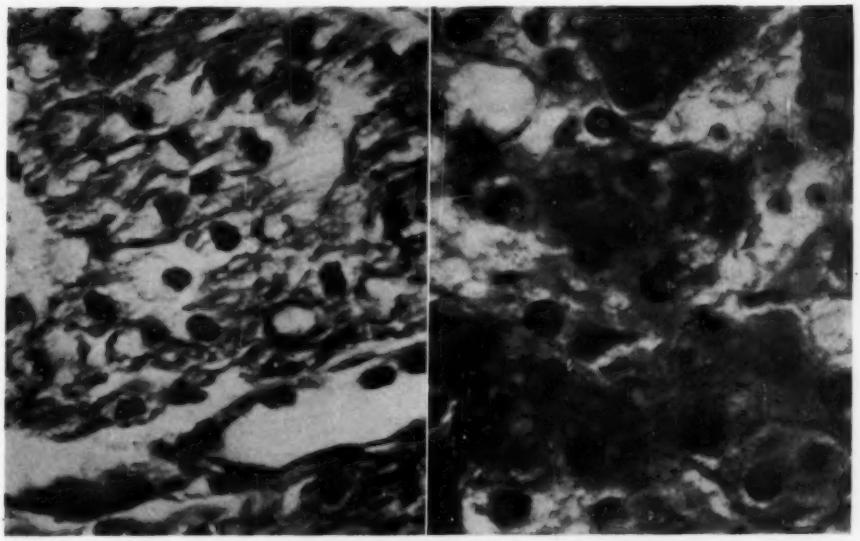

Fig. 1. Fig. 2.

Fig. 1.—Case 3. Heart muscle, showing vacuolar degeneration and interstitial edema.
Fig. 2.—Case 3, liver. Slight edema, evidenced by appearance of the spaces of Dissche. Vacuolar degeneration of liver cells of moderate degree.

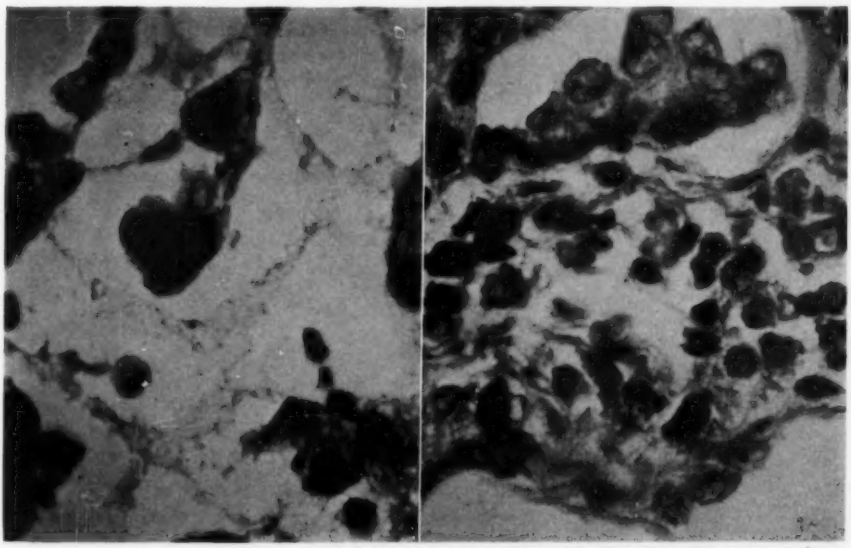

Fig. 3. Fig. 4.

Fig. 3.—Case 4, liver. Extreme edema; degeneration of liver cells.
Fig. 4.—Case 5, liver. Portal spaces show foci of myeloid cells, among them several eosinophiles.

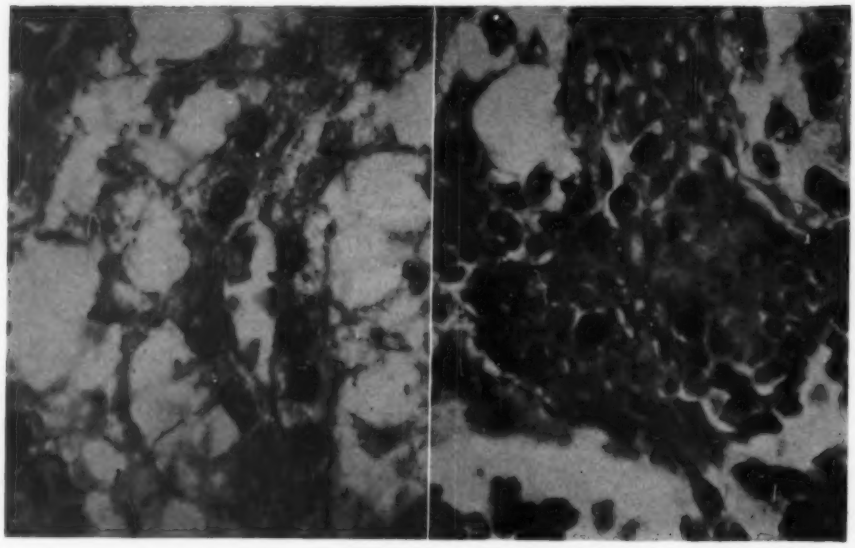

Fig. 5. Fig. 6.

Fig. 5.—Case 4, kidney. The tubules show severe degeneration of the lining epithelium.
Fig. 6.—Case 4, kidney. Packed red cells in a venule of the kidney cortex.

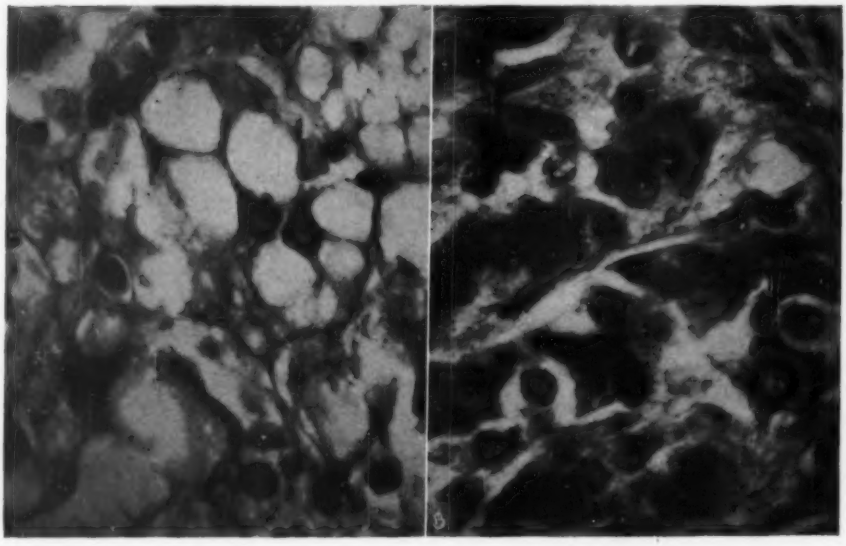

Fig. 7. Fig. 8.

Fig. 7.—Case 3, adrenal. Vacuolar degeneration of the cells of the adrenal cortex.
Fig. 8.—Case 4, adrenal. "Tubular degeneration" of the cell cords in the zona fasciculata.

In Case 4, an area of early focal necrosis was found.

The lungs of Case 3 showed aspiration of food, and in all cases acute emphysema was seen.

An interesting lesion was the presence of an unusually large number of *eosinophiles* in the myeloid foci of the liver in Cases 4 and 6; in Case 4, moreover, extensive infiltrations with eosinophiles were found in the muscularis of the stomach and of the urinary bladder.

DISCUSSION

Only one outbreak among newborn infants has been reported in recent years which compares in the severity of the disease and in the number of infected infants to our first outbreak. Guthrie and Montgomery[11] report sixteen fatalities among twenty-seven affected babies.

In our cases the most ominous sign was anuria, as can be seen in retrospect. All anuric infants died. Acidosis was another perplexing aspect. Two of the seven acidotic cases were fatal, but the others recovered. Loss of water and base in the stool could explain the acidosis in only two of the seven infants, and emesis occurred in only three of the acidotic infants. This led us to investigate urinary output and blood nonprotein nitrogen. All infants with acidosis showed an elevated nonprotein nitrogen, while the nonprotein was normal in four nonacidotic patients. In the *S. bareilly* epidemic, acidosis was present in three of the eight infants. Elevation of the nonprotein nitrogen was present in the two acidotic and one other infant.

Fever has been reported by Abramson and collaborators[3] and McKinlay[17] as characteristic of Salmonella infections of the newborn infant. In our observations, temperatures of 100° to 103° F. were found in four infants with *S. oranienburg* infection, nine had subnormal, and five had normal temperatures. In the patients with *S. bareilly* infection, none had fever and two had subnormal temperatures. Thus, only four out of twenty-six infants had fever while eleven had normal and eleven had subnormal temperatures. Differences in Salmonella strains and the characteristic lack of febrile response in the newborn infant probably account for the discrepancies.

Very remarkable was the occurrence of shock with low temperature in nine infants of the *S. oranienburg* series. No relationship could be found between the administration of Chloromycetin and shock, because it occurred in four patients who had not received Chloromycetin.

Clinical and post-mortem findings are in good agreement. The inflammatory lesions in the stomach and in the upper portions of the small bowel are characteristic of Salmonella infections as seen in older age groups—little has been published on the pathology in infants. The lesions in the stomach explain the frequency of vomiting, their absence in the colon explains the relative infrequency of severe diarrhea in the *S. oranienburg* cases. Degenerative visceral lesions are also well-known toxic effects of Salmonella infection, and they, in turn, substantiate the abnormal chemistry such as acidosis and azotemia. The clinical findings of shock correspond to the pathological findings of dilatation of the heart and of congestion in the visceral vessels, and of the interstitial edema in liver and heart muscle.

The lesions in the adrenal are those frequently seen in severe infections,

and they may have contributed to the appearance of shock and to the fatal outcome. For this reason desoxycorticosterone was given to the other infants.

The presence of large numbers of eosinophiles in the liver, stomach, and bladder of one infant poses difficult problems of interpretation. One might speculate whether there is a relation to the adrenal lesions, which were also most severe in this patient.

The combination of bacteriological and serological methods proved to be of great value. It enabled the laboratory to perform screening cultures on all infants in the nursery at the start of the outbreaks and to report their results in less than twenty-four hours. The use of tetrathionate broth greatly facilitated matters by sharply reducing the number of normal coliform organisms and by enhancing the growth of any pathogens.

The value of thorough serological classification is easily seen. On both occasions a Salmonella Group C_1 was isolated. Culturally, they were identical, and it was not until typing with flagellar antigens had been done that one could be sure that the second outbreak was unrelated to the first. The methods used are not complicated, and for bacteriological and epidemiological analysis they are easily within the scope of any diagnostic laboratory.

The two outbreaks are of interest because they point out the danger inherent in seemingly innocuous instruments (bottle warmer), and the danger of an infection brought in by an outside worker or by parturient mothers. Formula-fed babies are more easily exposed to Salmonella infection than breast-fed infants.[16] The outbreaks further show the importance of complete epidemiological and bacteriological analysis of every case and of all contacts. Finally, they demonstrate the ubiquitousness of Salmonella carriers among the general population, a very serious fact when it concerns hospital personnel.

In a recent paper Felsen, Weil, and Wolarsky[10] draw conclusions as to the proper management of situations as they may occur in hospitals. We endorse their recommendations of periodic stool examinations of all personnel assigned to the nursery and pediatric service, and to kitchen and dining rooms, and their further recommendation that all personnel with positive stool cultures be suspended from duty immediately, with pay, until they are clinically and bacteriologically free from infection. While we do not believe that it is feasible to obtain stool cultures before admission in all obstetrical cases, we consider it imperative to take frequent and periodic cultures of instruments and utensils in the nursery, and of food and utensils in the formula kitchen. We also endorse most emphatically Felsen and associates' recommendation that all preventive and control measures should be centralized under one authority in the hospital.

SUMMARY

1. Two outbreaks of Salmonella infection of the newborn infant are reported. The first outbreak, due to *S. oranienburg*, affected eighteen of the thirty-four exposed infants. Only eight of thirty-three infants exposed in the second outbreak became infected with *S. bareilly*.

2. The patients in the *S. oranienburg* epidemic were seriously ill, three fatally. The signs were, in order of frequency, diarrhea, emesis, shock, leucocytosis, cyanosis, acidosis, nitrogen retention and anuria. The patients in

the *S. bareilly* outbreak were only mildly ill. The most common signs were diarrhea, acidosis, and nitrogen retention.

3. Aureomycin was ineffective against *S. oranienburg* in doses of 25 mg. per kilogram. It may have been somewhat effective against *S. bareilly*.

4. In the three fatal cases due to *S. oranienburg*, the characteristic pathological lesions were those of acute gastroenteritis, of vascular damage, and of degeneration in the liver, kidneys, heart, and adrenals.

5. Epidemiological studies demonstrated that conclusions concerning the causation of a Salmonella outbreak can be drawn only after complete identification of the organisms is done in all cases. Many of the personnel were found to be harboring Salmonella strains unrelated to those causing infection in the infants.

6. Simple bacteriological techniques available to any hospital laboratory enable rapid identification of the cause and source of the infection.

7. Periodic cultures should be done at regular intervals on the stools of all personnel assigned to the nursery, pediatric service, and milk formula kitchen.

8. Frequent bacteriological checkups should be conducted of food, utensils, and instruments in the nursery and milk formula kitchen.

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Case Reports

HEMANGIOMA ASSOCIATED WITH THROMBOCYTOPENIC PURPURA

Report of a Case and Review of the Literature

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THE simultaneous occurrence of angiomatous lesions and thrombocytopenic purpura is unusual. Three cases have been reported in the literature. Kasabach and Merritt[1] reported an extensive capillary hemangioma of one leg and trunk associated with thrombopenia, the platelet count being 48,000 per cubic millimeter. The thrombopenia occurred before the hemangioma reached its peak. The rapid progression of the lesion plus the purpura suggested malignancy. A biopsy section was reported as a benign lesion. The patient was treated with x-ray therapy, radium therapy, and blood transfusions with striking beneficial results. A follow-up picture nineteen months later showed only the soft tissue contraction of the involved thigh.

Subsequently, Rhodes and Borrelli[2] reported a 6-month-old infant who at birth had a soft tissue mass on the back. Two months after birth the mass began to enlarge and the bleeding tendency became evident. The platelet count was reported as between 15,000 and 80,000 per cubic millimeter. A biopsy was reported as hemangioendothelioma. The patient was treated with x-ray irradiation and blood transfusions. The tumor regressed leaving a residual radiation fibrosis and the blood picture returned to normal.

The third case was reported by Silver and associates.[3] The patient was a 14½-month-old female who at birth had an elevated vascular area behind one ear. This lesion increased in size and new lesions appeared until there was extensive involvement of the skin of chest, neck, back, and arms. The thrombopenia appeared at the age of 20 months when the platelet count dropped to 42,000 per cubic millimeter. Earlier the patient had received several x-ray treatments without effect. Subsequently, the patient was treated with several transfusions but expired. The bone marrow smear in this patient revealed an increased number of agranular megakaryocytes.

The infant herein reported in detail is the fourth known case of hemangioma associated with thrombocytopenic purpura.

CASE REPORT

The patient, E. B. (K37779), a white female infant aged 21 days, was admitted to the University Hospital of the New York University-Bellevue Medical Center on April 21, 1950.

She was born at another hospital following an essentially normal gestation and delivery. Physical examination at birth revealed the left thigh to be enlarged approximately two and one-half times the size of the contralateral one. The left leg was edematous with ecchymosis extending from the inguinal region and buttock down to and including the foot. At birth,

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the bleeding time, coagulation time, platelet count, and complete blood count were within normal limits. Through a misunderstanding, vitamin K was given before any blood could be drawn for prothrombin estimation.

On the second day of life a bloody diarrhea began, but bleeding ceased twenty-four hours after vitamin K therapy was instituted. The diarrhea continued for one week, and the patient was treated with intravenous fluids. By the seventh day the ecchymosis and edema of the leg had disappeared, disclosing a mass 4 cm. in diameter, which previously had been obscured, on the lower inner aspect of the left thigh. Patient was discharged on the fifteenth day.

Three days later the left thigh suddenly began to enlarge and the overlying skin became a purplish-red in color. This spread down the leg and up on the buttock. During the next several days the ecchymosis became more intense and a petechial rash appeared on the extremity. The infant was admitted to the University Hospital on the twenty-first day of life.

The family history revealed that three siblings aged 3 to 5 years all had at birth strawberry marks at the hair line on the skin of the neck. One child developed a "blood blister" on his forehead at 9 months of age which was "coagulated." The histories of father and mother were essentially negative.

Physical Examination.—

General: The 21-day-old white female infant appeared acutely ill. The respirations were rapid and shallow; the temperature was normal. The patient was limp and lethargic, and the skin and mucous membranes were pale. The length was 74 cm., and the weight 3,200 grams.

Skin: Numerous small, red papules and petechiae were observed on the skin of the left leg and foot. These were most numerous on the skin of the left thigh. Over the inner aspect of the left thigh the skin was tense, brawny, and purplish-red in color. This color faded to a brighter red at the periphery. The skin of the left foot was slightly cyanotic.

There was a small, flat, pink capillary hemangioma on the skin of the nape of the neck at the hair line.

A healing wound was observed over the right internal malleolar vein.

Extremities: The left thigh was enlarged and measured 20.7 cm. in circumference while the normal right side measured 13 cm. in circumference. The skin was stretched tightly over the surface. The enlargement was firm, homogenous and slightly compressible. At the lower inner aspect there was a protrusion 4.5 cm. in diameter. The lower leg and foot were edematous and pitted on pressure. Femoral pulsations were normally palpable bilaterally. The dorsalis pedis and posterior tibial artery pulsations were palpated with ease on the normal right side but only the dorsalis pedis pulse was faintly palpable on the left side.

The liver edge was palpable. There were several large, soft lymph nodes measuring 0.5 to 1 cm. in diameter in each inguinal region.

The remainder of the physical examination (head, eyes, ears, nose, mouth, neck, chest, heart, urologic, eye grounds, and rectal) was normal.

The admitting laboratory data showed a severe anemia and pronounced thrombocytopenia, the platelet count being 25,000 per cubic millimeter. Prothrombin time determination was normal. The urine showed a very faint trace of protein and an occasional red and white blood cell.

Since the patient's condition was considered critical she was transfused before waiting for any further diagnostic studies.

Subsequent studies were as follows:

The bone marrow aspiration smears were quite cellular and revealed the usual variety of nucleated cell forms. These were present in the usual percentile distribution except for a slight increase in the number of lymphocytes, which was consistent with the age of the patient. An occasional megakaryocyte was encountered. These were not abnormal in form and pos-

sessed a granular cytoplasm. Scattered small groups of platelets were noted as well. The red cells did not present unusual changes. Diagnosis: Bone marrow smears—no pathologic diagnosis made.

bleeding time returned to normal in two days and the clotting time in four days.

This lesion presented a problem in differential diagnosis. A blood dyscrasia was evident: whether or

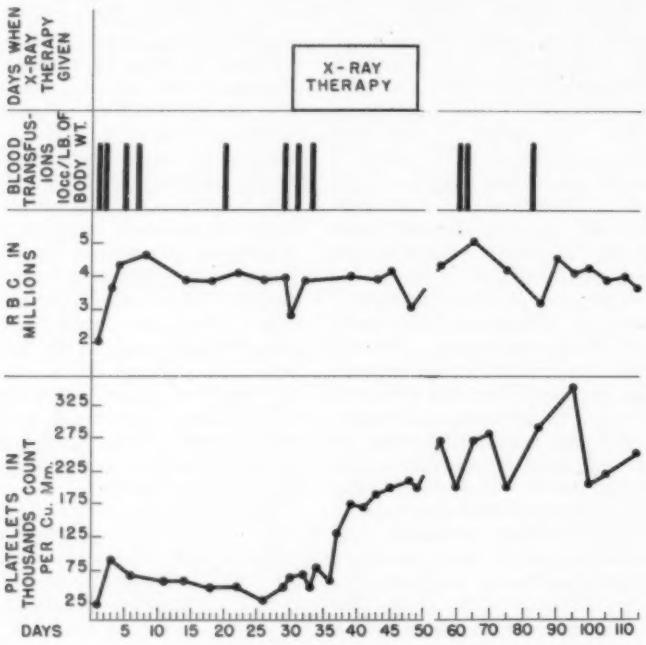

Chart I.—Illustrates the fluctuation in the platelet count per cubic millimeter and the red blood cell count in millions. Also indicated are the days when transfusions were given and the days during which x-ray therapy was administered. It is worthy to observe the fact that the platelets rose one week after the x-ray therapy was started.

X-ray of the thigh showed a soft tissue density throughout the entire left thigh. This was nonspecific in character and without definite x-ray characteristics for an etiological diagnosis. There was no osseous involvement. The Coombs test, Wassermann, chest x-ray, and long bone x-rays were normal. The variations of platelets and red blood cells are depicted in Chart I. The total white blood count and differential count are of little significance, having been normal for age. The initial bleeding time was thirty minutes and the clotting time of venous blood one hour. The

not the mass consisted of tumor and secondary hemorrhage or simple hematoma was the main issue. This lesion did not have the characteristics of a simple angioma or other tumor of the soft tissues. The x-ray showed the femur to be intact and to have no metastatic involvement.

Course.—The general status improved after the first two transfusions although the platelet count remained below 90,000 per cubic millimeter. After admission there was no further increase in size of the thigh and no further extravasation of blood. The patient was also given vitamin K, 4.8

mg. intramuscularly once a day, procaine penicillin (200,000 units intramuscularly daily) and a polyvitamin mixture.

On the second hospital day the tumor surgical consultants stated that although they suspected an underlying tumor, biopsy was interdicted by the bleeding tendency.

During repeated transfusions the swelling of the thigh decreased and there was some reabsorption of ecchymosis. The petechiae also began to disappear. Two weeks after admission all evidence of pitting edema and hemorrhage had subsided, once again revealing the underlying tumor which was now seen to have increased in size.

At this time the mass in the left thigh was a soft, protruding lesion which at its periphery faded into the soft tissues of the thigh. It was movable, nontender, compressible, and when compression released, it refilled with blood. It measured 8½ cm. in diameter and was purplish-red in color. There was a small, 1 cm. wide and 4 cm. long, cephalad extension of the main mass toward the femoral triangle. This gradually became more superficial until at its superior extent it presented in the skin over the femoral triangle as another small mass 2 × 2½ cm. (Fig. 1).

The clinical diagnosis still was not clear but it was decided to initiate x-ray therapy with the expectation that a rapid shrinkage of the mass would confirm the diagnosis of hemangioma. This was undertaken without biopsy because of the danger of uncontrollable hemorrhage.

X-ray therapy (Chart II) was given from May 20, 1950, to June 9, 1950. The tumor was cross-fired through two fields measuring 5 by 7 cm. each, and the beam was so directed as to minimize irradiation of the epiphysis for fear of eventual leg shortening. The factors were: 200 kv.; 50 cm. target—skin distance; half value layer 1.0 mm. copper. The skin dose was 2,400 r (measured with back scatter) to each of two fields. The total tumor dose was 3,360 r in twenty days.

At the end of this first week of therapy the mass had decreased by one-third of its former size. This rapid shrinkage tended to confirm the diagnosis of tumor. Hemorrhage would not have absorbed so rapidly. The tumor disappeared completely twenty-four days after the first x-ray treatment (Fig. 2). The platelets rose to a normal number one week after x-ray therapy was started. The rise also coincided with the initial decrease in the size of the tumor. The platelet count has remained normal until the present.

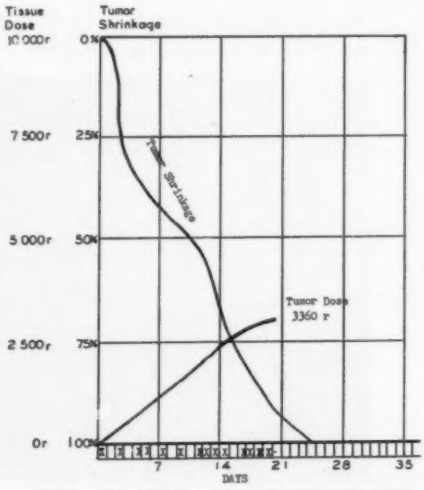

Chart II.—Graph of radiation therapy. Eleven deep x-ray treatments were given. The total tumor dose was 3,360 r in seventeen days. The tumor was very radiosensitive, shrinking rapidly at first (subsidence of edema) and then at a slower rate.

The cephalad prolongation of the tumor was not irradiated purposely so as to preserve tissue for biopsy.

On July 22, 1950, a biopsy was taken from the prolongation of the tumor. The procedure was uneventful. The histopathology was interpreted as follows: Sections show clusters of blood vessels infiltrating deeply throughout the subcutaneous fat. The blood vessels are of capil-

Fig. 1.—The lesion after blood transfusions and just prior to x-ray therapy. The edema and ecchymosis of the rest of the leg have subsided. The petechia has disappeared from the leg except on the skin overlying the lesion.

Fig. 2.—The tumor has disappeared at the completion of x-ray therapy. The tumor dose was 3,360 r. Note the superior extension which was not directly irradiated.

Fig. 3.—The involved leg seven months after treatment. The cephalad extension is represented by a small area of radiation fibrosis in the skin.

lary caliber for the most part although some are larger and tortuous in appearance. The vessel walls are extremely thin, apparently comprised almost exclusively of endothelial lining cells. The lining endothelium shows plump ovoid nuclei and scant indistinct cytoplasm. Between the vessels similar nuclei are encountered in moderate numbers. Mitosis average one per five high-power fields. Large amounts of fat lie between the clusters of blood vessels. Diagnosis: Hemangioma, predominately a capillary type.

After the biopsy was taken, the extension in the femoral triangle was irradiated. From Sept. 13 to 28, 1950, a skin dose of 2,400 r was given to a 5 × 7 cm. area which was contiguous with the previously irradiated area.

Over a period of seven months the tissues at the tumor site progressively contracted so that the soft tissue of the affected lower thigh are now smaller than the opposite normal side. This contracture is due to radiation fibrosis and to the defect produced by the tumor. To date, the left femur is radiographically normal.

At this time, the patient is progressing normally. There is no shortening of the affected leg and the patient is standing. When she attempts to walk there is a slight degree of external rotation of the affected leg (Fig. 3). Her weight gain, dentition, physical and mental development has been excellent. The complete blood count and platelet count are normal.

DISCUSSION

There are several clinicopathologic types of these tumors, each having a specific prognosis and radiosensitivity. It is difficult to establish clear-cut criteria in regard to malignancy. It is also difficult to predict the subsequent behavior from the microscopic appearance.

Malignant hemangioma of infancy is the most radiosensitive of the angiosarcomas and has a relatively good prognosis.

The mechanism which produced the thrombopenia in our case is not clear. We observed that the megakaryocytes did not appear abnormal at a time when the platelets were low. It was also noted (Chart I) that the platelets rose to normal one week after x-ray therapy was started. These facts suggest the thrombopenia was due to increased destruction rather than decreased production.

SUMMARY

A patient with a large hemangioma and an associated thrombopenia is reported. This is the fourth such case in the literature. The patient had a good result with blood transfusion and x-ray therapy.

The three cases previously reported are reviewed.

The authors wish to thank Dr. Herbert Willy Meyer and Dr. Alexander Zimmany of the Tumor Surgery Department, Dr. Maurice N. Richter, Director of the Department of Pathology, and Dr. Milton Friedman of the Radiology Department for their valuable assistance in the management of this case and the preparation of this paper.

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A CASE OF TURNER'S SYNDROME

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TURNER'S syndrome, especially in the male, is an interesting and rare occurrence. This syndrome was first described by Turner,[1] and consists primarily of a triad. The triad consists of a congenital webbing of the neck, a deformity of the elbow (cubitus valgus), and genital infantilism. Turner's original ten cases were observed exclusively in females from 15 to 23 years of age. Schneider and McCullagh[2] have also reported this triad occurring in females. The first case in a male was reported by Flavell[3] in 1943. His patient was 21 years old. The second case of Turner's syndrome in the male was that of a 3-year-old boy reported in 1948 by Dorff and associates.[4]

We have recently had the opportunity to observe and examine what we believe to be the third case of Turner's syndrome in a male.

CASE REPORT

R. H., a 7-year-old male child, was admitted to the hospital because he exhibited physical maldevelopment. This consisted of shortness of stature, a relatively enlarged head, flat feet, webbing of his neck, underdeveloped penis, and undescended testicles. His mother recalled that his neck and trunk had always appeared to be short and his head large. She stated that he had never grown as fast or as much as other children his age. For the past three years there had been practically no growth of the upper extremities. However, she had not noticed any associated weakness or fatigue.

The boy was born spontaneously after nine months' gestation. Respiration and cry were spontaneous, and no cyanosis was present. His birth weight was 7 pounds.

Developmental history revealed that he sat alone and began to cut teeth at 6 months of age. He talked at 12 months, and walked at 13 months.

The family history revealed no endocrine disturbances in either father, mother, or two brothers.

The patient's past history was negative for the usual childhood diseases.

On physical examination, the child's general appearance was that of dwarfed linear growth. He was 112 cm. tall and weighed 18 kilograms. His head was 54 cm. in circumference, and normal except for a hypoplastic mandible. The eyes exhibited a slight bilateral ptosis, but the pupils were equal and regular and reacted to light and accommodation. Fundoscopic examination was normal. The ears, nose, and throat examination was normal. The hair line extended well down the back of the neck. The neck showed bilateral webbing. The webs extended from the mastoid process to the acromioclavicular junction (Fig. 1). The thorax was normal and measured 56 cm. in circumference. The lungs were clear, and the heart was normal. Abdominal examination was negative. The testicles were undescended and nonpalpable, and the penis was abnormally small. The upper extremities showed moderate cubitus valgus, and were slightly underdeveloped. The lower extremities were short and showed a bilateral third degree pes planus. Neurological examination was negative.

The laboratory examination revealed a red blood count of 4.3 million with 13.6 Gm. of hemoglobin.

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The white blood count was 9,900 with 49 per cent neutrophiles, 48 per cent lymphocytes, and 3 per cent eosinophiles. The urinalysis was normal. A fasting blood sugar was 74 mg. and the glucose tolerance curve was normal. Chemical study of the blood showed: chlorides 103.0 meq per liter, calcium 4.6 meq per liter, phosphorus 4.5 mg. per cent, and phosphatase 4.7 Bodansky units. The 17-ketosteroids were 1.1 mg. per twenty-four hours by the method of Robbie and Gibson.

Fig. 1.

The urinary gonadotropins on two occasions were 6 mouse units by the method of Bradbury, Brown, and Brown. The electrocardiogram was normal. Roentgenograms of the skull, cervical spine, dorsal spine, pelvis, chest, and long bones were negative. Those of the wrist showed eight centers of ossification, or a bone age of 6½ years. A roentgenogram of the lumbar spine revealed a small spina bifida occulta on the fifth lumbar segment.

Psychometric examination revealed a mental age of 7 years, 2 months. The intelligence quotient was 106 or in the upper limits of the normal range.

DISCUSSION

When this case first came to our attention we were in doubt as to whether this syndrome would fall within the criteria as originally described by Turner. Our patient presented a small stature, webbing of the neck, undescended testes, underdeveloped penis, moderate cubitus valgus, and third degree pes planus. Lesser signs present were slight bilateral ptosis, mild micrognathia, underdeveloped arms, low hair line, and a spina bifida occulta.

These plus our laboratory and x-ray studies appeared to rule out those diseases which might be confused with Turner's syndrome. Such diseases include simple neck webbing, Klippel-Feil syndrome, Sprangel's deformity, cervical Pott's disease, and cretinism.

The urinary gonadotropins and 17-ketosteroid determinations were withnormal limits. Although Turner's original cases usually revealed an increased gonadotropin output, we felt that our patient, being of prepubertal age, would not show this sign. This was also noted in the case described by Dorff and collaborators.[4] It was further noted that Turner's cases were given chorionic gonadotropin in hopes of stimulating the sexual maturation, and two of his patients improved with this form of therapy. It was felt that if our case was testicular hypogenesis, rather than agenesis, a course of chorionic gonadotropin would prove valuable by causing the testes to descend and the penis to develop. Thus, prognosis would not be delayed on this aspect of the syndrome until after puberty. Therefore, the patient was given chorionic gonadotropin (A.P.L.) 100 units three times a week for six weeks. The 17-ketosteroid determinations were done frequently, but showed no change.

Within four weeks testicular descent was noted, and in six weeks the penis was perceptibly larger. This appeared to prove the prognostic value of gonadotropin therapy before puberty for this aspect of the syndrome.

SUMMARY

Turner's syndrome has been briefly reviewed and the third such case to occur in the male has been presented. A method of differentiating between testicular hypogenesis and agenesis at an early age has been discussed.

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PENICILLIN SENSITIVITY SIMULATING ATOPIC DERMATITIS

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SKIN manifestations of penicillin sensitivity are commonly seen, and clinical reports in this regard have been numerous. Included among the more common types of cutaneous allergic reactions to this antibiotic are the following[1, 2]: (1) urticaria and angioedema of the serum disease pattern and less frequently seen in association with an anaphylactic type of reaction, (2) the allergic contact type of eczematous dermatitis, (3) maculopapular eruptions, (4) the "id" reaction characterized by a delayed, erythematous papulovesicular type of eruption occurring in patients previously sensitized to dermatophytic fungi, (5) exfoliative dermatitis, (6) local indurated areas at the injection site, (7) erythema nodosum, and (8) purpura.[3] Recently a child was seen in whom a penicillin-sensitivity reaction closely resembling atopic dermatitis was observed. Since a rather thorough search of the literature including Brown's exhaustive review of the subject[1] confirmed the unusual nature of this reaction, it was felt that this patient's history was noteworthy of reporting.

CASE REPORT

A 2-year-old white female was referred for allergy consultation during April, 1950, with the suspected diagnosis of atopic dermatitis of two weeks' duration. About three weeks prior to the onset of this skin eruption, the patient had contracted a fever of unknown etiology. Prior to this she had been completely asymptomatic. Her physician had placed her on therapy consisting of oral penicillin (Penicillin Potassium Buffered Tablets, 50,000 units). When the fever failed to respond after two days, the therapy was changed to an oral sulfonamide preparation (a suspension of sulfadiazene, sulfamerazine, and sulfathiazole). Two days later a skin eruption appeared on the face. Since the fever already had subsided, chemotherapy was discontinued. Within the next two days the eruption spread to involve the neck, flexor surface of the elbows and knees, and the dorsum of the wrists. According to the description given, the dermatitis at the onset was erythematous—papular in nature.

Past history was entirely negative for infantile eczema, atopic dermatitis, hay fever, asthma, allergic rhinitis, urticaria, food intolerances, drug reactions, or any other associated allergic manifestations. She had received both penicillin and sulfonamide drugs on previous occasions with no untoward reactions. Family history was entirely negative for allergy.

Physical Examination.—When the child was first seen two weeks after the onset of the eruption, she presented the clinical picture of a dermatitis limited to the front and sides of the neck, flexor surface of the elbows and knees, dorsum of the wrists, and characterized by a pruritic erythematous papular eruption with lichenification, crusting, and slight oozing. Temperature was 99.6° F. (rectal). The remainder of the physical examination was otherwise normal. Laboratory studies revealed urinalysis negative, hemoglobin 12.5 Gm., red blood count 4.35 million, white blood count 13,050, polymorphonuclear leucocytes 22 per cent, lymphocytes 75 per cent, eosinophiles 2 per cent, basophiles 1 per cent.

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Therapy consisting of antihistaminic drugs, ephedrine sulfate, and topical dermatologic measures was then instituted. During the course of the following week the dermatitis subsided and completely disappeared. She was not seen until five weeks later when she again presented the identical eruption on the neck, flexor surfaces of the elbows and knees, and the dorsum of the wrists. Her mother stated that her skin had been perfectly clear for four weeks. However, she then developed an acute otitis media for which her physician gave her an intramuscular injection of 300,000 units of crystalline procaine penicillin. Twenty-four hours later, there appeared an erythematous papular eruption on the neck, flexor surface of the elbows and knees, and dorsum of the wrists. When seen one week later, the dermatitis had the same appearance as the original skin lesion previously described. Antihistaminic drugs and local dermatologic therapy were again prescribed and the dermatitis ran a course similar to that of the first episode, gradually subsiding during the next week. The dermatitis then disappeared, and repeated examinations during the following nine months have revealed her to be completely free of any similar or additional skin lesions.

COMMENT

When the child was first seen it was suspected that the dermatitis represented a drug sensitivity although proof of this was lacking. It was entirely possible that this skin eruption could have been a symptom of the original febrile illness of undetermined etiology. The rather short history of the lesion, its subsequent course, and absence of any evidence of atopy in the patient were against the diagnosis of an atopic dermatitis. Then again, if it were due to a drug sensitivity the etiological agent could have been either penicillin or one of the sulfonamide drugs. To distinguish between these on the basis of skin testing would have been extremely difficult. There is no satisfactory method for skin testing for sulfonamide sensitivity.[5] There has been a skin test described for penicillin sensitivity[6]; however, this has not proved to be too accurate a diagnostic aid. In addition, it was not felt that this measure was justifiable as long as the possibility of sensitivity to penicillin existed, in that the intradermal introduction of even 2,000 units of crystalline penicillin might flare up the dermatitis at this stage if its etiology were on this basis. However, the reappearance of the dermatitis upon the second administration of the penicillin and its subsequent disappearance implicates this antibiotic as the etiological agent. The short incubation period of the second reaction of only twenty-four hours following the administration of penicillin indicates that this later development represented an accelerated type of sensitivity reaction.

Atopic reactions due to penicillin have been described,[2, 4] so that a patient who is subject to asthma or hay fever and is allergic to penicillin may develop a paroxysm of asthma upon receiving this drug. Therefore, it would not be too unusual if a child with a history of atopic dermatitis were to have an exacerbation of the condition following the administration of penicillin or even if an allergic child were to present this type of skin lesion as a manifestation of penicillin sensitivity. The unusual and noteworthy point of consideration here is that the clinical picture of atopic dermatitis appeared in this instance, for the first time, as a manifestation of a penicillin reaction, in a nonallergic child with no evidence of an underlying atopy.

The appearance and distribution of this skin lesion was identical with atopic dermatitis and could easily have been mistaken for this latter condition. This serves to further illustrate the point that a diagnosis of atopic dermatitis cannot always be made on the basis of appearance and

localization alone and often must be differentiated from other dermatologic conditions such as allergic contact type of eczematous dermatitis and seborrheic dermatitis.[7]

SUMMARY

A case is presented in which a penicillin sensitivity reaction in a nonatopic child simulated the clinical picture of atopic dermatitis.

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Medical Progress

EVOLUTION OF SYSTEMIC RETICULOENDOTHELIOSIS IN CHILDHOOD

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SYSTEMIC reticuloendotheliosis is the proliferative response of the embryonal reticulum cells of the body to a stimulating agent. This specific response has been known for a long time in tuberculosis, syphilis, typhoid fever, and has recently been studied in histoplasmosis.[1] The stimulating agent is not known in Hodgkin's disease and in a group of pathological conditions such as Letterer-Siwe's disease, Hand-Schüller-Christian's disease, eosinophilic granuloma, and leucemic reticuloendotheliosis. These conditions have, therefore, been widely classified as idiopathic, or infectious, reticuloendotheliosis. However, Hand-Schüller-Christian's disease, in which cholesterol accumulation in the tissue is a dominant factor, was and is still classified in many textbooks with Gaucher's and Niemann-Pick's hereditary lipoidoses.

Systemic reticuloendotheliosis may take an acute, rapid course, terminating life within a few weeks, or months—and this usually occurs in infancy or early childhood. If this is the case, the clinical picture of Letterer-Siwe's disease,[2, 3, 4] characterized by generalized lymphadenopathy (Fig. 1), secondary anemia, occasional splenic and liver enlargement, purpura, fever, rapidly progressing cachexia, and a fatal outcome. It should be said here that according to a personal communication from Carl Smith,[5] New York, at least temporary improvement can be obtained in these cases by the administration of antifolic acid compounds. After their use, lymph gland swelling subsides and histiocytic proliferation in the bone marrow stops completely.

Reticuloendotheliosis may also be chronic and extend over many years —and this occurs usually in older children and in young adults. If this takes place, the clinical picture of Hand-Schüller-Christian's[6, 7, 8] (lipoid granulomatosis) disease results and, in many of these cases, the classical triad of exophthalmos (Fig. 2), diabetes insipidus, and bony defects, most frequently located in the skull (Fig. 3) can be seen.

Rowland[9] showed, as early as 1928 and 1929, that the histological lesions in Schüller-Christian's syndrome are identical in all involved organs. He stressed that there is a peculiar inflammation as shown by accumulation of eosinophilic and polynuclear leucocytes besides the proliferation of reticulum cells, histiocytes, foam cells, and the appearance of giant cells.

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Finzi,[10] in 1929, observed an eosinophilic granuloma which he regarded as a myeloma. Mignon,[11] in 1930, described a similar eosinophilic lesion in a 12-year-old boy, and, in 1938, Schairer[12] described two cases of "osteomyelitis with eosinophilic reaction." A detailed, beautifully illustrated histological report of several cases of "eosinophilic osteomyelitis" was published by Fraser[13] in 1935. He considered these lesions as a variant of lipoid granulomatosis. His report was the first classical description of the condition which was later called "eosinophilic granuloma of the bone" and regarded as a separate disease entity (Lichtenstein and Jaffe,[14] and Otani and Ehrlich[15]). Lichtenstein and Jaffe[14] applied this name to these lesions on account of the characteristic imprint which the eosinophiles gave it, though they recognized that its basic cells were histiocytes. These authors had observed, at this time, only solitary lesions and

Fig. 1.—Case M. J. Generalized lymphadenopathy in acute reticuloendotheliosis (Letterer-Siwe's type).

Fig. 2.—Chronic reticuloendotheliosis (Hand-Schüller-Christian's type). Asymmetric exophthalmos. (Thannhauser, S. J.: Lipidoses, Oxford University Press, New York.)

apparently were not aware of the extensive histological studies of Fraser,[13] and their opinion that eosinophilic granuloma was an entity of its own was applied to the numerous cases that were published in recent years, the most recent one by Weinstein, Frances, and Sprofkin.[16]

other organs in lipoid granulomatosis. They suggested that it should be regarded as a specific phase of the histological development of this condition and not as a new entity, because the dominance of eosinophilics is seen usually in the beginning while in later stages more and more xanthoma

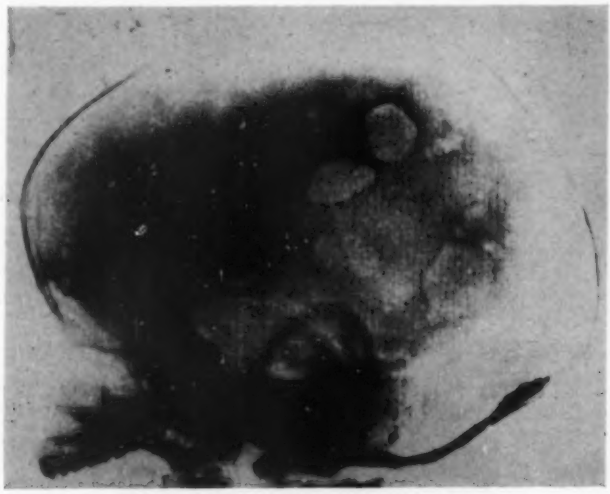

Fig. 3.—"Map skull." Case of acute lipoid granulomatosis. (van Crefeld, S., and ter Poorten, F. H.: Arch. Dis. Child. 10: 125, 1935.)

This form of reticuloendotheliosis is rather benign because there may be spontaneous healing and because these granulomas respond well to x-ray radiation and do not recur either after this treatment or after curettage. However, not even in this type is a definitely favorable prognosis justified, since there may be only a localized lesion at the onset, and later on either acute or chronic generalized reticuloendotheliosis may develop. The investigations of Farber,[17, 18] and Holm, Teilum, and Christensen[19] proved that the term eosinophilic granuloma comprised not only skeletal lesions but, also, the pathology of cells appear. A similar conception was also expressed by Troxler and Niemitz.[20] Thannhauser[21] stated that for the localized lesions, as well as for the generalized, the designation of "eosinophilic xanthomatous granuloma" is more appropriate than that of lipoid granulomatosis. The author mentions that this term does not embrace the important reticulo-histiocytic proliferation of early stages and it should be added that there are lesions where neither xanthoma cells nor eosinophilics are a dominant factor of the picture, so that the term reticuloendotheliosis may still be more suitable.

Green and Farber[22] stressed the anatomical relationship of eosinophilic granuloma of the bone to Hand-Schüller-Christian's and Letterer-Siwe's disease in ten of their own cases, and Lichtenstein and Jaffe,[23] in their second article on that topic, considered this postulate as a forward step toward the understanding of a larger subject. Guizetti's case[24] was the first to present a connecting link between eosinophilic granuloma of the bone and Letterer-Siwe's disease in a 3-month-old infant, and Mallory[25] added five cases of his own, showing the transition form from eosinophilic granuloma to chronic lipoid granulomatosis. Recently, Lapidus, Slobody, Germansky, and Willner[26] described three such cases, discussed the transition types to other forms of reticuloendotheliosis, and offered an extensive bibliography. Articles of Hertzog, Anderson, and Beebe,[27] Freud,[28] Bartels,[29] and Hansen,[30] who added five cases of his own, also stressed the unity of these three conditions.

The clinical pictures produced by the basic process of reticuloendotheliosis are so different that they have been classified as separate disease entities, such as Letterer-Siwe's disease, Hand-Schüller-Christian's disease, and eosinophilic granuloma of the bone. The pathological process in these cases, however, shows the same basic pattern. This goes so far that the pathologist would be unable to differentiate between a chronic and an acute form by examining tissue samples without receiving a clinical case history. Three phases of pathology can be seen:

(1) Proliferation of large, round monocytic histiocytes, or reticuloendothelial cells, which is accompanied by the appearance of giant cells (Fig. 4). Foam cells appear usually during this stage and elements of inflammation such as eosinophilic and polynuclear leucocytes can be seen. The origin of the histiocytes from the reticuloendothelial system (R.E.S.) can be shown by silver staining (Fig. 5) which reveals the characteristic fibers.

(2) The proliferating cells are short-lived, and spindle-shaped fibroblasts (Fig. 6) immigrate. During the transition stage, both round histiocytes and spindle-shaped fibroblasts are seen and giant cells may still be found (Fig. 7). There is a lack of vascularization in these areas during this phase and cell necrosis and hemorrhage can be observed.

(3) Fibrosis takes place, connective tissue replaces the areas of granulation, and, after a certain period of time, only scars can be seen in these spots.

If this process extends for some time, accumulation of free cholesterol and, especially, of cholesterol esters may occur within the histiocytes and accompanying giant cells, but there is hardly any cholesterol visible extracellularly during the first phase of proliferation. The cell protoplasm becomes foamy, and doubly refractile lipoid droplets, or crystals, can be observed with the polaroid microscope (Fig. 8). Fat stainings with sudan III or IV, or scarlet red, become positive at this time. During the second phase, when necrosis can be noted, cholesterol is liberated and can also be seen extracellularly in the form of clouds, droplets, or crystals.

The cholesterol accumulation in the granulating tissues put two problems before the early investigators: (1)

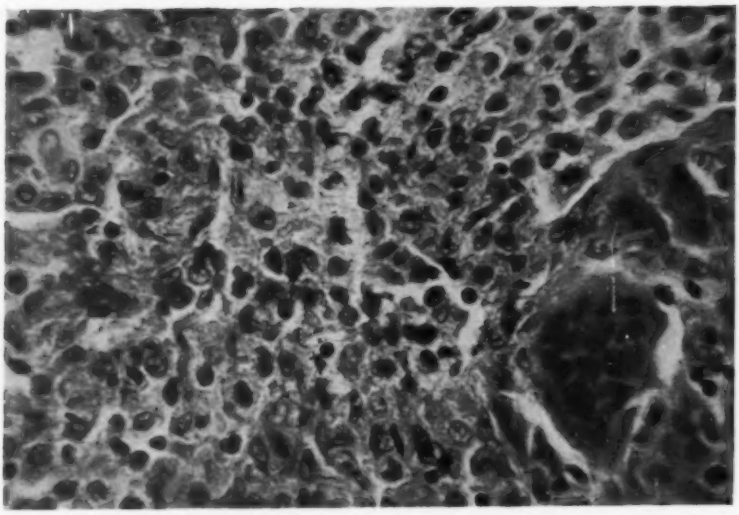

Fig. 4.—Case M. J. Lymph gland biopsy. Reticuloendotheliosis, phase 1: histiocytes and giant cells have replaced the lymphatic tissue. Cholesterol degeneration (foam cells). Acute case. (Freud, P., Grossman, L., and Dragutsky, D.: Am. J. Dis. Child. 62: 776, 1941.)

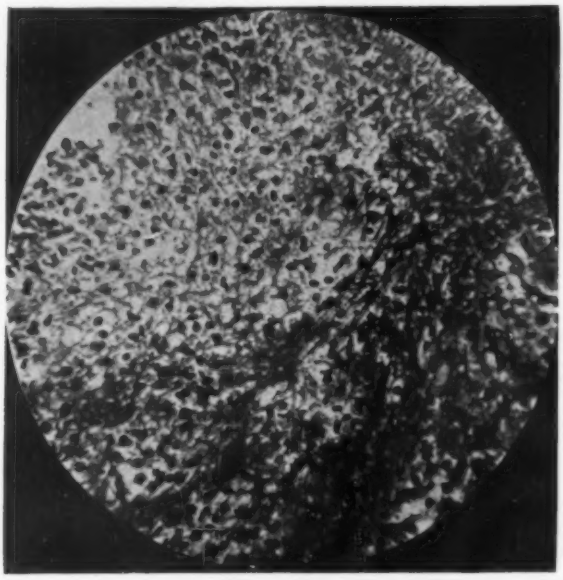

Fig. 5.—Case M. J. Lymph gland biopsy: acute reticuloendotheliosis. Silver staining showing reticular fibers of histiocytes. (Freud, P., Grossman, L., and Dragutsky, D.: Am. J. Dis. Child. 62: 776, 1941.)

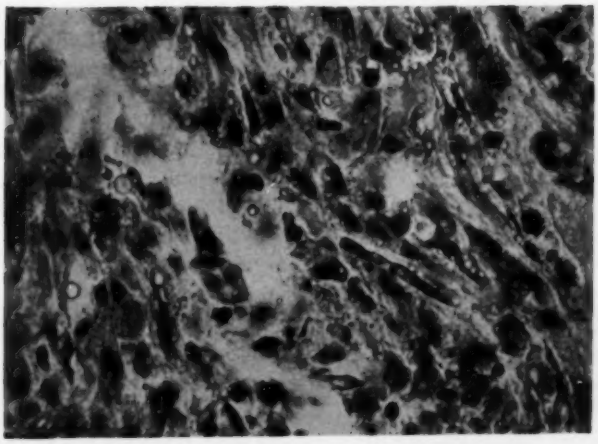

Fig. 6.—Case M. J. Lymph gland necropsy. Reticuloendotheliosis, phase 2: spindle-shaped fibroblasts have immigrated; cholesterol has been liberated by necrosis of histiocytes and can be seen extracellularly.

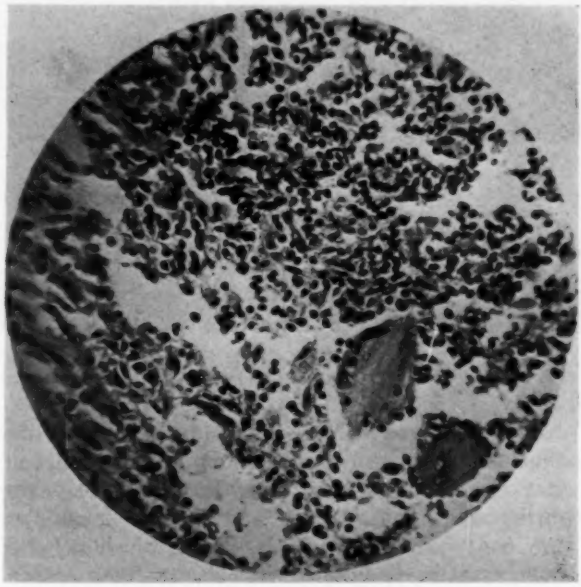

Fig. 7.—Case M. J. Lymph gland biopsy (acute case). Transition stage between phase 1 and phase 2 of the process. Histiocytes, spindle-shaped fibroblasts, and fat-laden giant cells visible.

concerning whether the cholesterol storage was primary and stimulated the proliferation of cells, and (2) whether the cholesterol was stored in these cells by the process of phagocytosis or by any other means. Rowland[31] expressed the view that lipoid reticuloendotheliosis was a primary lipoidosis and that cholesterol esters, by means of foreign body action, stimulated the granulation of reticuloendothelial cells. His opinion was widely accepted.[32] This theory led to the assumption that the condition was due to a disturbance of lipoid metabolism of the body and identical with the pathology of the lipoidoses such as Gaucher's and Niemann-Pick's disease. This view did not consider the fact that Gaucher's and Niemann-Pick's disease are hereditary, familial lipoidoses. In contrast to that, Hand-Schüller-Christian's disease is not hereditary and shows no familial or race tendency. It was therefore ssuggested that Hand-Schüller-Christian's disease, in which the cholesterol blood levels are always normal,[33] should be classified as a chronic type of reticuloendotheliosis and be removed from the chapter of the hereditary lipoidoses.[34, 35] The gap which resulted from this classification in the line of hereditary lipoidoses can well be filled in with the picture of essential familial xanthomatosis (xanthoma tuberosum), which is hereditary, resulting from a fundamental humoral disturbance of lipoid metabolism and characterized by hypercholesteremia and xanthomatous tumors in the skin, tendon sheaths and vascular system,

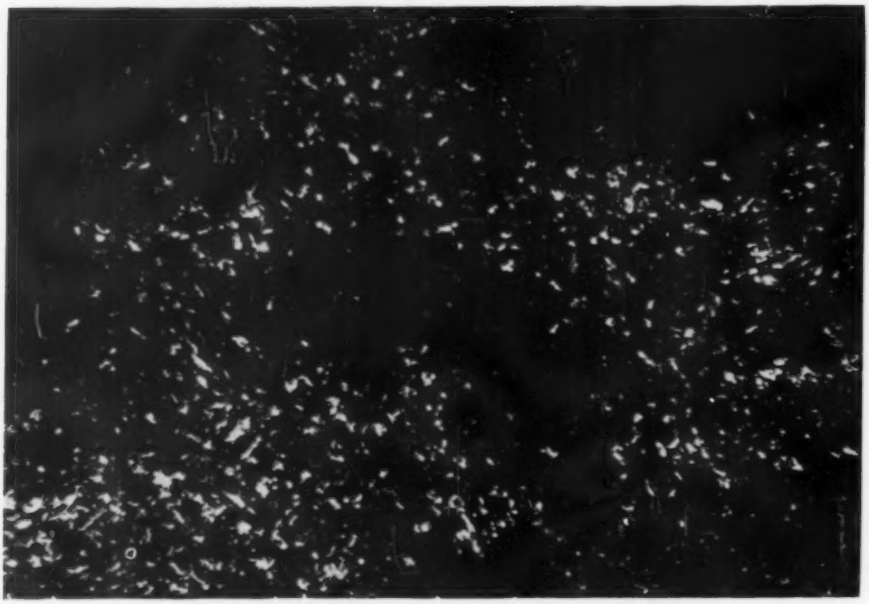

Fig. 8.—Case M. J. Lymph gland biopsy: acute reticulo-endotheliosis. Polaroid microscope: innumerable doubly refractile lipoid bodies visible. (Freud, P., Grossman, L., and Dragutsky, D.: Am. J. Dis. Child. 62: 776, 1941.)

and which, even in children, sometimes terminates with sudden death due to atherosclerosis or coronary occlusion. This condition was recently described in detail by Rigdon and Willeford,[36] who also offered an extensive bibliography.

Histiocytic proliferation in Hand-Schüller-Christian's disease does not only occur in the vicinity of cholesterol deposits but in areas far distant from these accumulations, and also without any lipoidosis.[2, 4] In cases of nephrosis or diabetes mellitus, where the serum lipoid levels are very high, no cell proliferation occurs. A classical example of this is the case of diabetes mellitus of Stahel-Stehli[37] in which large extracellular deposits of cholesterol crystals were seen in the tissues without any proliferative response.

Concerning the second problem, Rowland[31] believed that phagocytosis was responsible for the accumulation of cholesterol in the proliferating cells. However, the normal lipoid serum levels speak against this idea. In addition to that, the accumulation of cholesterol in the cells as a result of phagocytosis would only be probable if considerable amounts of the substance could also be demonstrated extracellularly and if intermediate stages of ingestion could be seen. This was never observed and, therefore, Letterer[2] concluded that the concept of storage does not necessarily mean entrance of the deposited substance into the cells from the outside, and Thannhauser,[38] in a personal communication, wrote that "as long as there is no softening of foam cells, the lipoids are found only intracellularly." He considers the cholesterol storage as a result of disturbance of intracellular metabolism of the proliferating cells.[39] We have compared the appearance of cholesterol in the proliferating cells with the process of fatty degeneration (fat phanerosis—cholesterol phanerosis).[40] Mallory[41] was the first to speak of lipoid degeneration, and we should like to suggest the term of cholesterol degeneration. The only difference between these two processes is that, in fatty degeneration, the saturation of cells with fatty substance is never as high as in cholesterol disease. Otherwise pathology seems to be the same.

The identity of the pathological process in acute and chronic forms of reticuloendotheliosis, the observation of cases that started as typical Letterer-Siwe types of this condition and terminated as chronic reticuloendotheliosis, such as the cases of Merritt and Paige,[42] and of Berg[43]; furthermore, cases of eosinophilic granuloma of the bone later developing either the rapid, fatal course of acute reticuloendotheliosis, or the chronic course of lipoid granulomatosis, have led to the opinion that these three clinical pictures are only different phases of the same basic process.

Variations of the pattern of reticuloendotheliosis may concern the chemistry, the histology, and the clinical pictures of this condition, but the similarity of the process led Grady and Stewart,[44] as early as 1934, to the statement that there may be a relationship between nonlipoid histiocytosis and Hand-Schüller-Christian's disease.

Wallgren[34] expressed the opinion that the paucity of lipoid storage in cases of acute reticuloendotheliosis is due to the rapidity of the course and not due to the fact that the acute and

chronic cases are separate disease entities. In the same year, Glanzmann[35] published an article in which he looks upon Hand-Schüller-Christian's disease as the chronic form and upon Letterer-Siwe's disease as the acute form of reticuloendotheliosis. He also believes that the formation of foam cells is a function of the duration of the condition and gives, as a minimum time, three months.

In 1941, Freud, Grossman, and Dragutsky[40] reported a case of acute reticuloendotheliosis (Letterer-Siwe's type) in a 7-month-old infant that showed all clinical criteria and the typical, rapid, fatal course. However, this was the first observation where, in an acute case, the cholesterol contents of the granulating tissues were as high as in chronic forms. While the normal cholesterol figure is about 0.62 per cent of dry tissue weight, the total cholesterol content of an affected lymph gland obtained by biopsy was 12.6 per cent in the third week after the onset of the disease, and the cholesterol content at necropsy five weeks later had risen to 17.9 per cent of dry tissue weight. These figures are identical with those found in chronic cases and, just as in these cases, the cholesterol serum levels were normal in this acutely ill infant (44 mg. per cent free cholesterol, 90 mg. per cent cholesterol esters, i.e., 134 mg. per cent total cholesterol). It was therefore concluded that this case was an actual link in the chain binding acute reticuloendotheliosis to the chronic types of lipoid granulomatosis.

Flori and Parenti,[45] in 1937, published a case in which biopsy demonstrated a nonlipoid reticuloendotheliosis, while autopsy, performed one year later, showed lipoid granulomatosis. The case of Freund and Ripps[46] showed, at the onset, generalized lymphadenopathy due to nonlipoid reticuloendotheliosis and, seven months later, developed bony defects with lipoid granulomatosis, and the case of Love and Fashena[47] closely resembled this case. If these patients had died before the development of lipoidosis, their condition would have been classified as acute nonlipoid reticuloendotheliosis. Since then, numerous articles have appeared supporting the idea that Letterer-Siwe's disease and Hand-Schüller-Christian's disease are only different phases of the same process. Havard, Rather, and Faber[48] came to the same conclusions, presenting a patient of their own who, in addition to the classical features, also presented leucopenia, thrombocytopenia, and severe edema and ascites associated with hypoproteinemia. Other papers were offered by Lichty,[49] Currens and Propp,[50] Versiani, Figueiro, and Junqueira,[51] and by Imler,[52] who also suggested that these diseases may be an infectious type of reticuloendothelial cell granuloma. Here it should be mentioned that M. Bass,[53] of New York, according to a personal communication, observed three cases of acute, fatal, nonlipoid reticuloendotheliosis in siblings of infant age. Compared with all the other case reports, however, no definite conclusions can be drawn concerning the possibility of heredity of the condition.

The lymphatics are more frequently involved in the acute cases, the skeleton usually in chronic cases, but the patients of van Crefeld and ter Poorten,[54] and of Foot and Olcott,[55] show that extensive skeletal involvement

may also occur in the acute case. Involvement of the lungs also is usually seen in the chronic cases, but again van Crefeld's case,[54] the case of Currens and Propp,[50] and our own case[40] show that this may happen in the acute type.

Siwe,[56] in a recent article, expressed the opinion that Letterer-Siwe's disease and Hand-Schüller-Christian's disease are separate entities and that it is an oversimplification of the problem to consider them only as different types of the same condition. He stresses that the acute process stops at the histiocytic proliferation stage, while the chronic process develops into fibroblastic granulation with lipoid storage, but it should be said that, apart from the very rapid, fatal cases of reticuloendotheliosis in patients who died within a few weeks so that there was no time for fibroblastic response, only one case is known where the process stopped with histiocytic proliferation. This is Foot and Olcott's patient[55] with histiocytic proliferation lasting for sixteen months and very little fibrotic response. Siwe,[56] furthermore, states that if there is cholesterol accumulation at all in the acute cases, it is only a minimal amount, and mentions as an example the cases of Gross and Jacox.[57] This has been disproved by our own case[40] with its extremely high lipoid tissue content. Finally, Siwe[56] expresses the opinion that the infectious agents causing the different clinical entities of reticuloendotheliosis are unknown and that they may be different in each of the types. This cannot be disproved but the unknown stimulating agents—infectious or not—lead to identical tissue changes.

The clinical criteria are not only variable due to the duration of the course but depend largely on what organs are affected. In chronic cases, where there is extensive bony involvement, the children may complain of pains very similar to those found in rheumatic fever, spontaneous fractures may occur in Hand-Schüller-Christian's type of the condition or,

Fig. 9.—Case P. C. Eosinophilic granuloma of the humerus with spontaneous fracture. (Willner, M. M.: Bull. New York Med. Coll. 9: 45, 1946.)

more frequently, in the eosinophilic type. The x-ray picture cannot be differentiated from that of malignant bone tumors, but biopsy reveals the peculiar eosinophilic lesion (Fig. 10). The skin overlying bony defects may become affected.

Polydypsia and polyuria are regular features of Schüller-Christian's syndrome. The specific gravity of the urine is mostly around 1.010. This rather high figure does not conform with the conception of true diabetes insipidus. However, the anatomical involvement of the pituitary stalk as well as the hypothalamic region with proliferating tissue, as in the case of

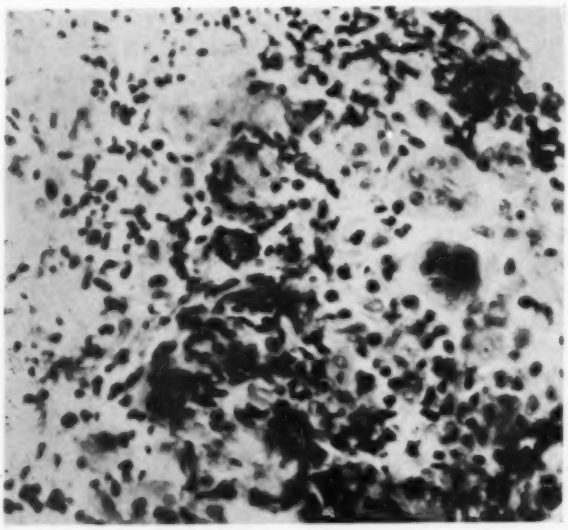

Fig. 10.—Eosinophilic granuloma. Many eosinophilic leucocytes, histiocytes, and giant cells. (Case of M. M. Willner.)

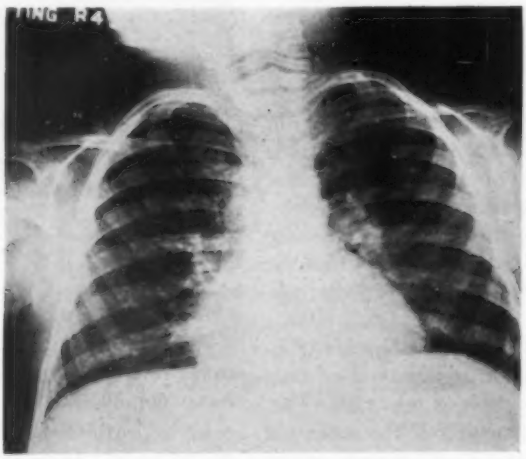

Fig. 11.—Case J. M. Picture resembling miliary tuberculosis of the lung. (Chronic reticuloendotheliosis with leucemic response.) (Case presented in this paper.)

Thompson, Keegan, and Dunn,[58] is sufficient proof for a real diabetes insipidus, which symptoms sometimes may subside temporarily to reappear subsequently.

In cases where the lungs are involved, cough and fever, and sometimes cyanosis, x-ray findings simulating that of miliary tuberculosis (Fig. 11), of atelectasis (Fig. 12), or pneumonia, and even of cavity formation (Fig. 13) are found.

The typical skin lesion in lipoid granulomatosis is xanthoma disseminatum. If this skin lesion is the only localization of the condition, as frequently seen in infants and young children (xanthoma juvenile), the le-

Fig. 12.—Case M. J. Acute reticuloendotheliosis: atelectasis of the left lung due to compression of left main bronchus and infiltration of lung tissue by granulating masses. (Freud, P., Grossman, L., and Dragutsky, D.: Am. J. Dis. Child. 62: 776, 1941.)

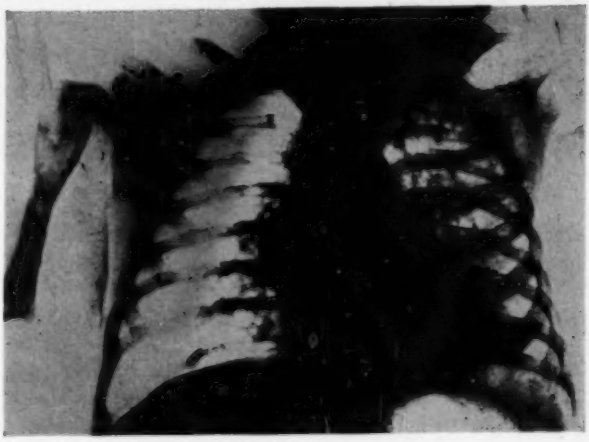

Fig. 13.—Honeycomb structure of lungs. Large bony defect in right humerus. Case of acute lipoid granulomatosis. (van Crefeld, S., and ter Poorten, F. H.: Arch. Dis. Child. 10: 125, 1935.)

sions are discrete, vary in size from a pinhead to an almond, and usually do not occur in clusters as in cases of generalized lipoid granulomatosis. They can be differentiated from hereditary xanthomatosis (xanthoma tuberosum) by the fact that the cholesterol serum levels are always normal in this condition.[39] The lesions consist of slightly raised, smooth, sometimes peeling maculopapular patches of lemon or café-au-lait color, and may affect any part of the body, including the scalp. Here the lesion frequently resembles seborrheic dermatitis showing a yellowish tint. There is no itching. In some cases half pea-shaped, yellow nodules are seen (Fig. 14). In these patients, the prognosis is rather benign just as in the localized eosinophilic granuloma of the bone (Thannhauser: Monosymptomatic Lesions of Skin or Bone[59]). However, nothing definite can be said of the further development since there is a possibility that organs other than the skin may be affected by the condition. Such a case was reported by Lamb and Lain.[60] Pasey and Johnston,[61] Spillman and Watrin,[62] and Turner, Davidson, and White[63] described cases where they observed, during the course of xanthoma disseminatum, diabetes insipidus (brain involvement), and a peculiar type of lung fibrosis. Sometimes, also petechia-like lesions are seen such as described by Horsfall and Smith[64]

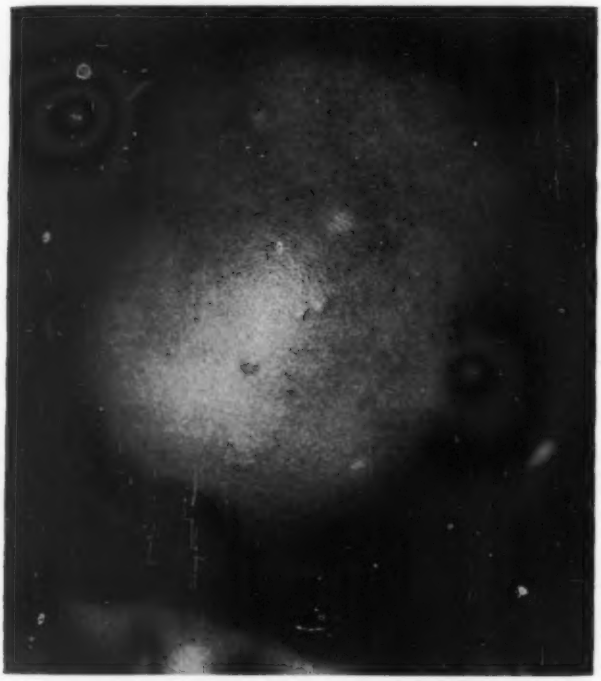

Fig. 14.—Case J. M. Xanthomatosis of scalp. Large hemorrhagic lesion on forehead.

and by Lane and Smith.[65] These lesions look exactly like petechiae but, histologically, they can be recognized as xanthomatous. In addition to xanthomatosis of the skin, many of the chronic cases and almost all acute ones develop skin petechiae. The purpuric spots may become discolorated and frequently appear within the area of xanthomatosis. The diagnosis of xanthomatosis should be confirmed by a biopsy. Skin lesions consisting of erythema, eczema-like lesions, and pinhead-sized nodules were also reported in cases of nonlipoid reticuloendotheliosis such as in the two patients of Varga, Richter, and De-Sanctis.[66] Similar cases were reported by Hand,[67] Herzenberg,[68] Hausman and Bromberg,[69] Hoefer,[70] Chiari,[71] Rothnem,[72] Wheeler,[73] Lustora,[74] Stoos,[75] Gigon,[76] Lesné, Lièvre, and Boquieu,[77] Auslander,[78] Wayson and Wiedman,[79] Twining,[80] Sweitzer,[81] and Berg.[43]

Our knowledge is still very spotty about the fourth type, reticuloendotheliosis with leucemic response. Downey[82] states "that in leucemic reticuloendotheliosis there is an irreversible hyperplasia of the reticuloendothelium in which the free cells are differentiating toward some type of blood cell other than the monocyte." In these cases, the architecture of the bone marrow, the lymph nodes, and sometimes the spleen, liver, lungs, and intestines, is considerably changed by proliferation of "stroma cells." Normally, there are relatively few of these large mononuclear reticular cells. In reticuloendotheliosis, they dominate the histological picture due to profuse proliferation. This type of hyperplasia can well be differentiated from ordinary leucemia where there is a hyperplasia of the myeloid or lymphatic cells, respectively.[85]

Many authors consider monocytic leucemia and some cases of myelogenic leucemia as a form of reticuloendotheliosis. This opinion is opposed by Levine[83] and by Forkner.[84] They state that it was never proved that the monocytes originate from the R.E.S. and, therefore, regard monocytic leucemia as a separate entity. In contrast to them, Goldzieher and Hornick[85] state that the origin of the monocytes from the reticuloendothelial cells has definitely been proved and that these cases are due to leucemic reticuloendotheliosis. They base this opinion on reports such as the cases of Merklen and Wolf,[86] and of Dameshek,[87] where the lymph nodes, spleen, and liver were enlarged and the normal architecture of the lymph nodes and spleen affected by intense proliferation and infiltration of large mononuclear cells, and the cases of Ewald,[88] Krahn,[89] Ugrimnov,[90] Wyschegorodzowa,[91] Schwirtschewskaja,[92] and Bykowa.[93] Bohne and Huismann[94] published a similar observation, and Bunting[95] reported two cases of leucemia that had its origin in the lymph nodes. Grenet, Levent, and Isaac-George[96] described two such cases in children 2½ years of age. The diagnosis of this condition becomes still more difficult because mixed leucemias occur: myeloid leucemia in which there are considerable numbers of monocytes as well as myelocytes. There seem to be two forms, one arising directly from the R.E.S. (Schilling type), also known as leucemic reticuloendotheliosis, and the other with a more rapid course, arising from the myeloid tis-

sues (Naegeli type). This latter type shows both monocytes and myelocytes in the blood and generally terminates as myeloid leucemia. In a number of cases, the pathologieal cells seen in the peripheral blood stream and in the bone marrow, and in areas of proliferation, are so primitive and young that nothing definite can be said of whether they are early forms of monocytes or myelocytes.

Giffin and Watkins[97] state that in some of these cases, primitive free reticuloendothelial cells may be found in the blood in addition to the reticular type of the monocyte. The primitive cell is usually larger than the leucocyte and usually has an eccentric nucleus which is frequently elongated and may be rounded, or indented. In the opinion of these authors, this is the most important diagnostic element. Montgomery and Watkins[98] described in detail five cases of leucemia, two of them with reticuloendotheliosis. They particularly stress a primary autochthonous cutaneous origin and differentiate between cases where skin lesions occur at the onset of the condition and cases where skin lesions are only terminal.

Thelander, Crane, and Lanman[99] described a case of xanthoma disseminatum in an infant starting at the age of 3 months. About three months later, the child developed a blood picture suggestive of myeloid leucemia and bone marrow findings confirming this diagnosis. The condition terminated fatally after twenty-three months. Lipoid granulomatosis was found in lymph glands, spleen, liver, bone marrow, lungs, intestines, and pericardium. This was the first case report where xanthomatous lesions initiated leucemic reticuloendotheliosis, and this fits well into the postulate of Montgomery and Watkins[98] that there may be an autochthonous skin origin of reticuloendotheliosis with leucemic response. Additional light may be shed on this condition by the following report:

CASE REPORT

J. M., a 2-year-old white male, was admitted to the Flower and Fifth Avenue Hospitals on Feb. 4, 1949, with the chief complaints of a cold for one month, abdominal distention, and an orange-colored rash over the body. The family history was irrelevant. Physical examination revealed acute rhinopharyngitis, otitis media, hypertrophied tonsils overlapping at the midline, acute moderate lymphadenitis, and acute bronchitis. There were orange-colored and elevated lesions, varying from 1 to 3 mm. in diameter, scattered over the body, forehead, neck, and trunk (Fig. 14). There were also brown macular lesions on the trunk measuring 3 to 10 mm. in diameter (café-au-lait spots).

The past history revealed that the child was admitted to Bellevue Hospital on Sept. 5, 1948, and discharged on Oct. 15, 1948, the diagnosis being acute nasopharyngitis, acute purulent otitis media, and xanthomatosis of the skin. A biopsy on Sept. 29, 1948, revealed xanthomatosis (typical foam cells). There were no bony defects noted.

The blood counts taken during the time of acute respiratory infection were: (Sept. 5, 1948) hemoglobin 13.0 Gm.; erythrocytes 4,500,000; leucocytes 19,750 with a differential count of 38 mature polymorphonuclear cells, 7 staff polymorphonuclear cells, 52 lymphocytes, and 3 monocytes. On October 2, hemoglobin was 11.5 Gm.; erythrocytes 4,800,000; leucocytes 13,700 with a differential count of 57 mature polymorphonuclear cells, 14 staff polymorphonuclear cells, 11 lymphocytes, 3 mono-

cytes, and 25 eosinophiles. There was no sign of any leucemic response. The serum cholesterol levels were rather high: (September 14) cholesterol 303 mg. per cent; cholesterol esters 199 mg. per cent; (October 7) cholesterol 249 mg. per cent; cholesterol esters 172 mg. per cent.

On Feb. 22, 1949, small nodes in the axilla and inguinal areas were noted. The spleen was palpated 1½ finger-breadths below the left costal margin. A blood smear at that time revealed "neutrophiles-stab cells 10 per cent, segmented 15 per cent, lymphocytes 50 per cent, monocytes 20 per cent,

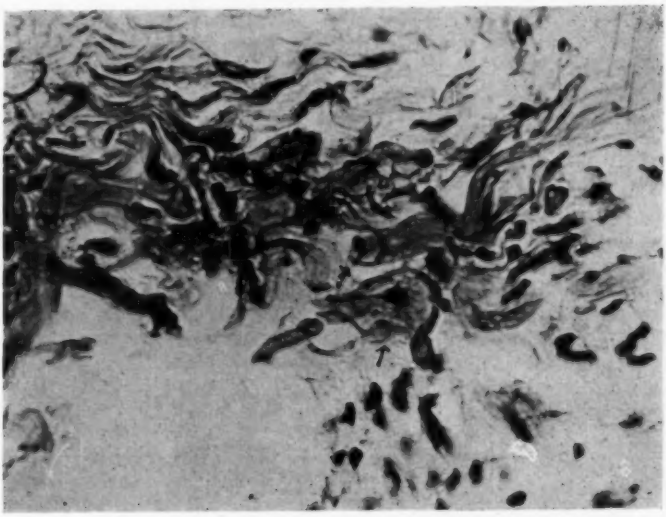

Fig. 15.—Case J. M. Skin infiltration with large macrophages with foamy cytoplasm.

Another biopsy of a papule in the lumbar area, performed at the Flower and Fifth Avenue Hospitals on Feb. 25, 1949, again showed skin infiltration with large macrophages with foamy cytoplasm, proving the diagnosis of xanthomatosis (Fig. 15).

Bone marrow study on Feb. 10, 1949, revealed the marrow to be very hyperplastic. On February 24 there was little essential difference in the myelogram from that reported on February 10, but in comparison, the promyelocytes were higher and the normoblasts were lower; the diagnosis of a leucemic response was still doubtful at this time.

The results of the study of the peripheral smears are revealed in Table I.

eosinophiles 1 per cent, abnormal lymphocytes 2 per cent, promyelocytes 1 per cent, and myeloblasts 1 per cent (100 cells counted). Smear showed a sprinkling of neutrophilic myelocytes, and rare myeloblasts."

On March 28, 1949, the child had his tonsils removed and a marked diminution of the nasal discharge followed.

Other laboratory tests revealed the microsedimentation rate to vary from 15 to 17 mm.; prothrombin time 16.6 seconds; heterophile antibody negative; stool examination for ova and parasites negative; Bence-Jones proteinuria negative; the fragility test showed initial hemolysis to start at 0.422 per cent NaCl and hemolysis to be completed at 0.302 per cent NaCl;

TABLE I

DATE	% HB.	R.B.C.	W.B.C.	NEUT. MAT.	NEUT. IMMAT.	EOSINOPHILES	BASOPHILES	LYMPHS MAT.	LYMPHS IMMAT.	MONOCYTES	METAMYELOCYTES	MYELOCYTES	PROMYELO.	PLATELETS
2/ 7/49	74	4.24	21,350	21	13	2	1	38	3	11	4	7	--	--
2/18/49	75	4.4	59,400	17	7	3	1	31	15	15	5	6	--	--
2/24/49	--	--	27,900	26	15	1	3	42	7	6	--	--	--	290,000
2/25/49	70	4.1	47,800	34	6	6	0	28	4	11	2	6	--	--
3/ 4/49	--	--	54,000	35	2	1	0	38	4	16	4	4	--	--
3/ 8/49														230,000
3/16/49	--	--	36,000	24	4	2	1	52	5	12	0	0	--	--
3/25/49	62	3.7	47,200	16	11	3	0	35	10	9	6	9	--	--
4/ 1/49	56	3.4	27,000	34	10	2	1	32	0	7	5	9	--	--
4/ 4/49	55	3.27	42,000	27	18	0	1	16	6	14	8	5	--	--

urine smears and cultures were negative; the Wassermann test was negative; repeated urinalyses were negative; nonprotein nitrogen 50 mg. per cent (later repeated 32.43 mg. per cent); fasting blood sugar 68.7 mg. per cent; cholesterol 199 mg. per cent; cholesterol esters 112.2 mg. per cent; icteric index 5 units; bilirubin 0.97 mg. per cent; total proteins 7.56 mg. per cent (albumin 4.60 mg. per cent, globulin 2.96 mg. per cent); alkaline phosphatase 17.3 King-Armstrong units; cephalin flocculation test negative; thymol turbidity test 4 units; calcium 10.2 mg. per cent; phosphorus 3.21 mg. per cent; hematocrit 37.3; stool examination for free fat negative; bleeding time 3 minutes, 35 seconds; coagulation time 4 minutes, 15 seconds.

X-ray of the chest on Feb. 7, 1949, revealed thickened hilar shadows with peribronchial infiltration most marked in the bases, which have the appearance of bronchiectasis. On February 25, x-ray of the chest showed some decrease in the hilar thickening and infiltration. On March 24, there was little change in the appearance of the chest since the previous examination.

X-ray of the skull and long bones on March 5, 1949, showed some minimal osteoporotic change in the femur, tibia, and bones of the foot. No other evidence of bone pathology was noted.

The child was discharged on April 8, 1949, with the diagnosis of (1) leucemic reticuloendotheliosis; (2) rule out chronic myelogenous leucemia and xanthomatosis.

The infant was readmitted to Flower and Fifth Avenue Hospitals on Nov. 22, 1949, for further work-up and was discharged on Dec. 27, 1949. The physical examination was essentially the same as that noted on the previous discharge except that the liver was now palpated 3 fingerbreadths below the right costal margin and the spleen was palpated 3 fingerbreadths below the left costal margin.

The results of the study of the peripheral blood smears are revealed in Table II.

Other laboratory tests included: repeated urinalyses negative; cholesterol 128 mg. per cent; esters 86 mg. per cent; microsedimentation rate varying between 20 to 26 mm. an hour; stool examination for ova and parasites negative; stool culture negative.

Bone marrow study on Nov. 28, 1949, revealed the marrow to be very hyperplastic, showing an absolute increase in myeloblasts and promyelocytes and a slight increase in eosinophiles. The mature granulocytes were

TABLE II

DATE	% HB.	R.B.C.	W.B.C.	NEUT. MAT.	NEUT. IMMAT.	EOSINOPHILES	BASOPHILES	LYMPHS. MAT.	LYMPHS. IMMAT.	MONOCYTES	METAMYELO.	MYELOCYTES	PROMYELO.	BLASTS
11/22/49	62	3.45	42,600	22	18	1	2	28	5	19	2	3	2	--
11/24/49	63	3.55	76,000	27	8	4	1	15	4	9	10	13	7	2
12/10/49	70	3.7	79,000	37	2	0	0	31	7	0	4	16	3	--

TABLE III

DATE	% HB.	R.B.C.	W.B.C.	NEUT. MAT.	NEUT. IMMAT.	EOSINOPHILES	BASOPHILES	LYMPHS MAT.	LYMPHS IMMAT.	MONOCYTES	METAMYELO.	MYELOCYTES	PROMYELO.	PLASMA CELLS
3/19/50	50	2.7	141,500	25	6	1	0	19	0	7	15	17	7	
4/5/50	46	2.3	124,000	37	2	1	0	16	0	6	12	15	7	
4/15/50	63	3.15	87,000	36	4	3	2	16	0	11	5	15	3	
4/18/50	46	2.35	63,800	34	2	2	0	18	0	7	8	12	8	
5/11/50				25	15	4	0	14	0	29	0	7	5	1
6/6/50	65	3.95	66,800	32	6	9	2	15	0	3	10	8	6	7

normal. There was a relative decrease in the normoblasts and erythroblasts. A diagnosis of chronic myelogenous leucemia was suggestive with some reservations.

Liver biopsy done on Dec. 6, 1949, reported "liver tissue showing cloudy swelling, hydropic degeneration and fatty infiltration. There was an inflammatory cell aggregation around the bile canalieuli."

X-ray of the chest on November 23 revealed "a definite thickening of the hilar shadows with a fine miliary infiltration extending into both lung fields especially marked in the bases. These findings may be compatible with leucemic or xanthomatous infiltration" (Fig. 11). On December 13, x-ray of the chest revealed "a slight decrease in the thickening of the hilar shadows previously reported and the fine miliary infiltration extending into both lung fields."

X-ray of the long bones on Dec. 2, 1949, revealed "transverse lines of increased density observed at the distal metaphyseal end of the femur and the proximal metaphyseal end of the tibia. The epiphyseal development is compatible with a chronological age of 3 to 4 years. No evidence of osteal or periosteal pathological process is observed."

The infant was discharged on Dec. 27, 1949. He was again readmitted to Flower and Fifth Avenue Hospitals on March 29, 1950, because of fever, croupy cough, and substernal retractions. The laryngotracheobronchitis was cured with steam, ipecac, and penicillin. At that time a few changes in the physical examination were noted. The abdomen was more distended, with the liver being palpated 4 fingerbreadths below the right costal margin; the spleen was palpated 3½ fingerbreadths below the left costal margin; new xanthomatosis lesions were seen in the scalp. They were orange in color (similar to the ones noted on other parts of the body previously), slightly elevated, measuring 2 to 5 mm. in diameter. There were about eight of these lesions noted in the scalp. The cervical

nodes were somewhat enlarged, discrete and firm in consistency.

The results of the peripheral blood smears during this admission are revealed in Table III.

Primitive large cells with indented eccentric nuclei, as described by Giffin and Watkins,[97] were seen in the blood stream (Fig. 16). The blood counts done in this case clearly show that there are spontaneous remissions and relapses independent of blood transfusions. This is typical for reticuloendotheliosis with leucemic response.

especially marked at the bases." (Fig. 11.)

X-ray of the abdomen on April 4, 1950, revealed "haziness in upper portion of abdomen, which is probably due to marked enlargement of the liver and spleen."

X-ray of the long bones on April 4 revealed the same as that taken on Dec. 2, 1949.

Bone marrow examination on April 14, 1950, by Dr. Peter Vogel revealed "total nucleated count 205,000 per cubic millimeter; megakaryocytes 88 per cubic millimeter; differential

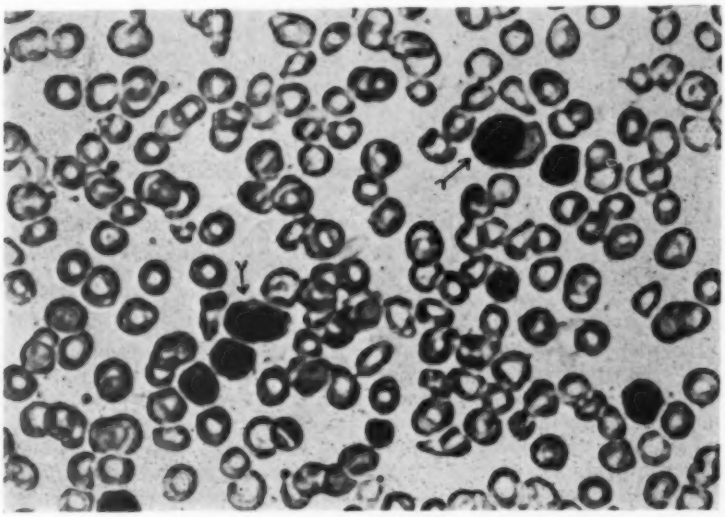

Fig. 16.—Case J. M. Extra large primitive cells with eccentric, indented, and elongated nucleus (arrows). (Case presented in this paper.)

Other laboratory data were as follows: Microsedimentation rate varied between 19 and 30 mm.; urinalyses were repeatedly negative; stool culture was negative; repeated Mantoux series were negative; blood cholesterol was 101 mg. per cent, and esters 36.2 mg. per cent.

X-ray of the chest done on March 30 and April 4, 1950, revealed the same findings observed at previous examinations: "Fine miliary infiltration extending into both lung fields,

—promyeloblasts 43 per cent, myeloblasts 5.3 per cent, myelocytes 1.7 per cent, eosinophilic myelocytes 3.0 per cent, nonsegmented neutrophiles 8.3 per cent, segmented neutrophiles 5.7 per cent, eosinophiles 5.0 per cent, basophiles 1.7 per cent, lymphocytes 3.0 per cent, hematogones 1.3 per cent, erythroblasts 1.3 per cent, and normoblasts 21.7 per cent.

X-ray radiations were started on April 4, 1950:

	PARTS USED	TOTAL R PER FIELD
1.	AP—thorax	67
2.	Lat. thorax	67
3.	AP—spleen	312
4.	Lat. spleen	258
5.	PA—spleen	304
6.	AP—pelvis	54
7.	L and R femur	54

X-ray treatment was finished on July 31, 1950.

On May 11, 1950, bone marrow aspiration revealed the following: total nucleated count 1,000,000 per cubic millimeter; megakaryocytes 55 per cubic millimeter; differential—myeloblasts 3.0 per cent, myelocytes 36.0 per cent, eosinophilic myelocytes 2.0 per cent, nonsegmented neutrophiles 18.0 per cent, segmented neutrophiles 10.0 per cent, eosinophiles 4.0 per cent, lymphocytes 2.0 per cent, hematogones 16.0 per cent, reticulum cells 0.5 per cent, erythroblasts 0.5 per cent, and normoblasts 8.0 per cent.

These bone marrow findings are those of a leucemia, but of an unusual type, in an infant this age. These findings were compatible with the entity called leucemic reticuloendotheliosis.

Dr. Dargeon examined the infant on April 20, 1950, and it was his impression that this was a case of "xanthomatosis (lipid) reticuloendotheliosis with leucemic response."

On April 26, 1950, a biopsy was done of an enlarged inguinal lymph node. Microscopic study of several sections of lymph node showed moderate alterations in nodular irregularity. The sinusoids were largely filled by endothelial cells and there were also small and large reticulum cells. The endothelial cells showed moderate sized vesicular nuclei and a small amount of nonvacuolated cytoplasm. There were three types: a few large reticulum cells with large nuclei and small amount of slightly basophilic cytoplasm, a large number of small reticulum cells with small amount of granular cytoplasm, a significant number of these cells resembling the lymphoblasts seen ordinarily in the germinative centers of the primary follicle. In addition, here and there a polynuclear cell and eosinophile

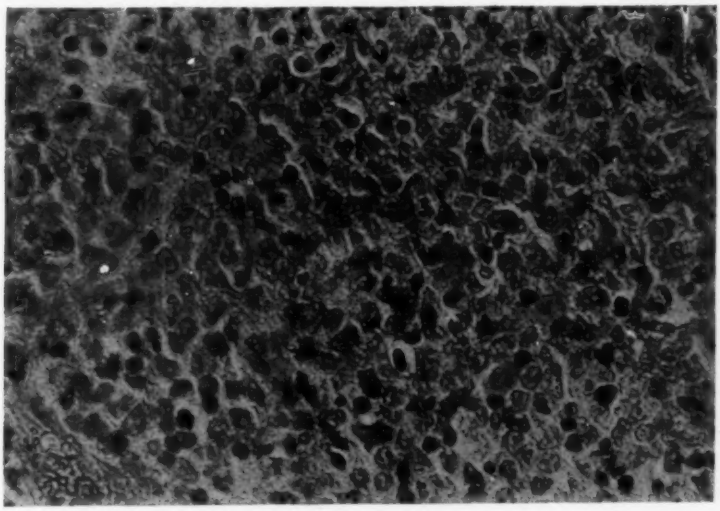

Fig. 17.—Case J. M. Lymph gland biopsy: profuse reticuloendotheliosis altering the physiological picture.

were noted. None of the reticulum cells showed evidence of significant lipid storage or foamy cytoplasmic changes, except for some cells in the peripheral sinuses (Fig. 17).

Until the middle of July, the child was running a downhill course in spite of transfusions and the administration of antifolic acid compounds. Nosebleeds and bleeding from the rectum became more frequent and showers of skin petechiae were observed. At this time, the child was very pale and feeble. Subsequently, the bleedings gradually subsided, the child became more active, his appetite improved, he was gaining weight, and gradually went into a remission. This remission was confirmed by the improvement of the blood picture (Table IV).

TABLE IV

DATE	% HB.	R.B.C.	W.B.C.	NEUT. MAT.	NEUT. IMMAT.	EOSINOPHILES	BASOPHILES	LYMPHS MAT.	BLAST CELLS	MONOCYTES	METAMYELO.	MYELOCYTES	PROMYELO.	PLATELETS
7/5/50	63	- -	26,600	39	7	4	4	15	4	20	3	3	1	270,000
7/24/50	78	4.5	20,600	33	0	-	2	23	3	25	2	4	-	150,000
7/28/50	80	- -	21,800	36	3	3	2	34		22	1	-	-	85,000
8/7/50	84	4.69	25,200	37	7	9	2	21		15	2	5	4	80,000
8/21/50	65	4.06	23,400	42	5	7	1	28		10	1	5	1	80,000
9/19/50	70	4.2	34,800	46	5	2	-	29		8	2	5	3	165,000
9/27/50	80	4.1	26,400	35	3	5	2	35	1	16	1	2	-	70,000
10/18/50	70	3.7	46,000	32	21	2	-	48	2	2	-	2	-	140,000

On Oct. 19, 1950, bone marrow count revealed the following figures: total nucleated count 820,000 per cubic millimeter; megakaryocytes 22 per cubic millimeter; differential—myeloblasts 10.3 per cent, promyelocytes 1.3 per cent, neutrophilic myelocytes 17 per cent, eosinophilic myelocytes 2.3 per cent, neutrophilic metamyelocytes 9 per cent, eosinophilic metamyelocytes 1.3 per cent, neutrophilic band forms 12 per cent, eosinophilic band forms 0.6 per cent, polymorphonuclears 10 per cent, eosinophiles 0, basophiles 0.3 per cent, lymphocytes 11.3 per cent, monocytes 2.0 per cent, reticuloendothelial cells 0.3 per cent, megakaryocytes 0.3 per cent, pronormoblasts 3.0 per cent, erythroblasts 2.3 per cent, and normoblasts 17 per cent.

Both peripheral counts and bone marrow examination still revealed the presence of a myelogenic leucemia but with greatly improved figures.

On Oct. 25, 1950, the patient was discharged strikingly improved. He was seen regularly in the clinic for blood counts and bone marrow controls.

On Jan. 16, 1951, the child was readmitted with the chief complaints of four severe nosebleeds prior to admission. Physical examination at this time revealed a chronically ill, very pale child with a markedly distended abdomen. There were numerous small and large ecchymotic areas scattered over both lower extremities. The xanthomatous skin lesions were unchanged and a few new ones had appeared.

Positive physical findings: Weight 35¼ pounds. Generalized lymphadenopathy: large freely movable, slightly tender lymph nodes were present in both anterior cervical chains, in the axilla, and in the inguinal regions. The abdomen was markedly distended, tense, but not rigid. The liver edge was palpable five fingerbreadths below the costal margin, sharp, but not nodular. The spleen could be felt six fingerbreadths below the costal arch near the pelvic

brim. The spleen was firm and slighly tender.

On the day of admission, his blood count revealed hemoglobin 57 per cent, color index 0.7, red blood cells 4,100,000; white blood cells 111,000 with neutrophiles 90 per cent, eosinophiles 3 per cent, and lymphocytes 7 per cent. Neutrophilic series included myelocytes 34 per cent, promyelocytes 2 per cent, and metamyelocytes 8 per cent; platelets 150,000; cholesterol 114.4 mg. per cent; esters 35 mg. per cent. On Jan. 20, 1951, hemoglobin was 55 per cent, color index 0.7, red blood cells 3,700,000; white blood cells 114,000 with neutrophiles, 78 per cent (myelocytes 6 per cent, promyelocytes 19 per cent, metamyelocytes 8 per cent), eosinophiles 11 per cent, lymphocytes 9 per cent, and monocytes 2 per cent.

It can be seen that the white blood cell figures, which from July to October, 1950, ranged from 20,000 to 40,000 white blood cells, had now gone up to 114,000. On Jan. 18, 1951, the bone marrow was very cellular. There were many myelocytes and promyelocytes and blast forms. Megakaryocytes were practically absent. The nucleated red blood cells were moderately reduced. The following figures were obtained from this bone marrow count:

Total nucleated count 850,000 per cubic millimeter; total megakaryocytes 0; myeloblasts 9 per cent; promyelocytes 2 per cent, neutrophilic myelocytes 5 per cent; eosinophilic myelocytes 4 per cent; basophilic myelocytes 1 per cent; monocytes (monocytoid forms) 10 per cent; neutrophilic metamyelocytes 4 per cent; eosinophilic metamyelocytes 1.5 per cent; band forms 4.5 per cent; polymorphonuclears 7 per cent; eosinophilics 0.5 per cent; basophilics 0.5 per cent; lymphocytes 9.5 per cent; pronormoblasts 1.5 per cent; basophilic normoblasts 9 per cent; polychromatic normoblasts 22 per cent.

A second series of x-ray radiations was started on Jan. 19, 1951, to the spleen with 108 R per field. At the time of this writing, the child is becoming progressively weaker and running a downhill course. The further outcome of the process will be reported.

COMMENT

It is interesting to note that early investigators gave classical descriptions of different types of reticuloendotheliosis but believed that they belonged to well-known disease entities. Borissowa[100] described a case of acute reticuloendotheliosis with all its typical criteria as a case of Banti's disease. Hand[6] thought that his case of chronic lipoid granulomatosis was a peculiar case of tuberculosis. Jaffe and Lichtenstein[14] and, independently of them, Otani and Ehrlich,[15] believed that eosinophilic granuloma of the bone was a new entity. Only Fraser[13] diagnosed his case of "eosinophilic osteomyelitis" as a variant of Hand-Schüller-Christian's disease. Even after the different clinical forms of reticuloendotheliosis had been described by the original authors,[2, 3, 4, 6, 7, 8, 14, 15] it took a long time before cases belonging to these groups were generally recognized. Giant-cell sarcoma, Hodgkin's disease, tuberculosis, and other conditions were frequent faulty diagnoses. With the growing knowledge of the pathology of these conditions, more and more cases were reported showing that this condition is not as rare as was originally believed.

The striking difference in the clinical pictures and the fact that it became known relatively late that cholesterosis may also occur in acute cases, made the understanding of the relationship of the different types very difficult. During recent years this has been overcome, many transi-

tion forms have been reported, and the majority of the authors now agree that, in spite of the great variety of clinical criteria, these types are only variants of the same basic process. Some authors (Siwe,[56] Lanman[99]) still believe that the conditions are separate entities and base this opinion mainly on the hypothesis that the agents stimulating proliferation are of a different infectious etiology. However, even if this is true, it can be said that the pathological process is identical in all types.

to these diseases. Tschistowisch and Bykowa[101] define reticuloendotheliosis as systemic proliferation of mononuclear cells which conform to undifferentiated embryonal elements. Accordingly, they regard reticular structure as the most diagnostic criterion.

Klemperer[102] agrees with this opinion by stressing that in this process any group of embryonal mesenchymal cells (hematic, phagocytic, endothelial, or fibroblastic) may participate. Proliferation of these cells is seen

Fig. 18.—Case J. M. Lymph gland biopsy: profuse reticular proliferation. Capsule of lymph node intact.

The present conception of reticuloendotheliosis does not accurately conform with Aschoff's definition of the R.E.S. as a group of cells with phagocytic properties. Only if one considers this group of cells in a wider sense, including all mesenchymal embryonal cells with and without phagocytic abilities, can the term of systemic reticuloendotheliosis be applied chiefly in the lymph nodes, bone marrow, spleen, and liver but, by further progress, the skeleton itself, lungs, or any other organ may be affected. Also, the question will arise whether this process is only hyperplasia (inflammatory), or whether neoplastic growth of this cell group should be included. Frequently an exact border line between hyperplasia and neo-

plastic growth cannot be drawn. This is especially true in cases of reticuloendotheliosis with leucemic response. In the case presented in this paper, it is interesting to note that, for a long time, there was only xanthomatosis of the skin. Later on, leucemic phenomena developed, and only after these had lasted for about one year, was reticuloendotheliosis found in a lymph gland. The capsule of the lymph node was completely intact and in spite of profuse proliferation, there was no tumorlike growth (Fig. 18). In contrast to these findings is the case of Gittins and Hawksley[103] where reticulum-cell sarcoma of the ovary and monocytic leucemia were found in a 2½-year-old child. This illustrates the possibility that similar pictures may be caused by hyperplasia and neoplastic growth as well.

Chronic myelogenous leucemia in young children has rarely been seen. Cooke[104] reported three patients, two of whom died after fourteen months and two years' duration, respectively, but both children were older than 9 years. Dale,[105] who reviewed a series of seventy-one leucemia cases in children, observed one patient who was still living at the time of his publication, two years after the onset of the condition. Again, the child was 9 years of age. The patient of Thelander[99] and our own case are rare reports on chronic myelogenic leucemia in children of this very young age group. One is well justified in calling these cases chronic leucemias by adhering to the definition of Baar[106] that leucemia should only be regarded as acute when, with its sudden onset, all the severe criteria of the condition are present and when the condition terminates fatally after a few weeks or months.

In July, 1950, Thannhauser[107] wrote in a personal communication: "I have wondered very often why we did not see, at least sometimes, an increased white cell count in eosinophilic xanthomatous granuloma similar to that we see once in a while in Hodgkin's disease."

In the cases of leucemic reticuloendotheliosis reported up to now no lipoid degeneration has been found and it was unknown whether there was a relationship between these cases and lipoid granulomatosis. Thelander's[99] case and our own answer this question in a positive sense. They show that xanthomatosis may be accompanied or followed by leucemic phenomena just as nonlipoid reticuoendotheliosis.

SUMMARY

1. The relationship of acute reticuloendotheliosis (Letterer-Siwe's type) to chronic reticuloendotheliosis (Hand-Schüller-Christian's and eosinophilic types) has been discussed.

2. It has been suggested that Hand-Schüller-Christian's disease be removed from the chapter of hereditary lipoidoses (Gaucher and Niemann-Pick) and to fill this gap with hypercholesteremic familial xanthomatosis (xanthoma tuberosum).

3. Cholesterosis has ben discussed and reasons have been brought forward as to why this process should be termed cholesterol degeneration.

4. An attempt has been made to define the term of reticuloendotheliosis as accurately as possible.

5. Reticuloendotheliosis with leucemic response has been discussed. A new form of systemic reticuloendo-

theliosis characterized by xanthomatosis and leucemic phenomena has been described in detail and has been classified with the known types of this condition.

6. The literature concerning the relationship of the different types of systemic reticuloendotheliosis has been reviewed.

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Psychologic Aspects of Pediatrics

PROJECTIVE TESTS IN THE PERSONALITY INVESTIGATION OF CHILDREN

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PROJECTIVE techniques have been developed in an effort to understand the hidden motives and repressed forces that underlie human behavior and are responsible for many of the seeming contradictions in human activity. The tests seek to project out these underlying forces in a way that will reveal their causes and what needs they are serving. Projective techniques are useful diagnostic aids. They are, however, no substitute for the comprehensive medical and psychiatric approach necessary for the evaluation of a child's problems.

THE RORSCHACH TEST

The projective tests most commonly in use are the Rorschach Test, the Thematic Apperception Test, and the Children's Apperception Test. The Rorschach Test consists of ten inkblots, printed upon a white background and mounted on cardboard 7 by 9½ inches. Five of the blots are grayish black, two are black and red, and three are multicolored. The blots are numbered one to ten and are presented to the subject in order.

Test instructions are simple and consist of the following statement: "I am going to show you some inkblots and I want you to tell me what they look like to you, what they might be. Just tell me everything you see." Nothing is said about the basis on which interpretation is to be made. The subject is not told to use the entire blot or parts of it. No mention is made of the possibility of using color in the interpretation, whether the interpreted forms should be seen as static or moving, or whether the shading should be considered or just the outline of the blot. Similarly, no indication is given as to what the content should be, or of the number of interpretations to be made, the position in which the card is to be held, the time to be used and so on. If the subject asks for information on any of these points he is given only noncommittal answers. In other words, the aim of the investigation is to place the individual in a situation where there are no clues as to expected behavior, thereby compelling him to develop the circumstances in his own way. The assumption underlying this procedure is that an individual resorts to his habitual forms of behavior when left to his own devices and must draw on his past experiences, his abilities and habit patterns in these conditions.

In evaluating the subject's responses to the test various aspects of the personality and the interplay between these come into consideration. Important here are the degree of emotional control and maturity that has

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been attained and the methods employed for maintaining this, the personality resources the individual has at his disposal, his attitudes toward himself and others, that is his social development, as well as a number of other variables.

To obtain this information, each interpretation is examined under three main headings: the area of the blot that was used in making the interpretation, the particular aspects of the blot that determined the response, and the actual content of the response. The frequency with which an individual interprets the entire blot reveals the extent to which he is willing and able to deal with the total situation. An individual giving many responses which include the entire blot is certainly reacting very differently from one who chooses only small peripheral details in making his answers. The first individual is willing to take account of all aspects of the situation with which he is confronted, the second is choosing from it insignificant aspects which he thinks he can handle and which answer his particular needs. The areas most often chosen for interpretation by older children and adults are the large sections into which the blot seems to divide itself, and the person responding primarily to such areas is one who is aware of the usual, the obvious, and the commonplace.

The form of the blot is the basis on which interpretation is most frequently made. When a subject employs the form alone for his answer he is drawing on his intelligence and his past experiences. He compares the shape of the blot with his mental image of the object he is interpreting and decides whether or not such an interpretation is appropriate. To do this he must have had some experience with the object he is interpreting and be able to recall it with accuracy. All the processes involved here are mental ones. However, when the subject introduces color into his interpretations, his emotions have entered the picture. Whether the color is allowed to dominate the perception or is subordinated to the form reveals the degree of emotional control and maturity the subject has attained. The individual who does not use color at all is regarded as either overcontrolled, depressed, or emotionally flat, in contrast to the individual who uses color whenever possible, pointing to emotional spontaneity and possible instability.

Fig. 1.—(Courtesy Hans Huber, Bern, and Grune & Stratton, New York.)

Introducing movement into the blot, that is, seeing the figures which are being interpreted as in action, is a creative act and reveals the presence of fantasy activity. The nature of this activity can be determined by the type of response that is given, as well as by the relationship between this form of answer and other test responses. A child who interprets all human and animal figures as fighting and compet-

ing probably has an aggressive fantasy life which may be in marked contradiction to his overt behavior. Many children stress oral activties, seeing birds about to be fed, wolves on the prowl seeking prey. This emphasis on food frequently betokens a sense of deprivation on an emotional rather than a physical basis. Some indulgence in fantasy is a positive sign, indicating a valuable resource for handling frustrations. However, too much fantasy, especially where there is no emotional spontaneity in the form of color answers, indicates withdrawal of contact with the outside world.

Since the blots lend themselves to the interpretation of animal forms it is only natural that about one-half of the responses are animal in content. The nature and variety of the other concepts offered by the subject give some indication as to his interests and preoccupations. Some responses betray the individual's feelings of hostility to others as in the following response: "A dead man, all torn up, someone killed him, smashed him." Others indicate strong exhibitionistic trends in interpretations of "aerobats, doing tricks, dancers on a stage," and so on.

The number of times each test factor is used is determined and compared with the frequency of other test factors. The ratios thus obtained can be translated into personality descriptions. For example: In a record where there are four movement interpretations and only one color interpretation, the ratios of M:C is 4:1 and the conclusion to be drawn is that, regardless of what his overt behavior may seem to indicate, the child giving such a record is more responsive to his fantasy than to external pressure and has little inclination toward establishing emotional contact with his environment.

CASE 1.—An 8-year-old boy is failing in school and is adjusting very poorly at home. He is constantly getting into unnecessary difficulties and does not seem to profit by experience or punishment.

The Rorschach record consisted of the following:

Total number of responses	16	
No. of responses using the entire card	2	(12½%)
No. of responses using large areas	8	(50%)
No. of responses using minute areas	6	(37½%)
No. of responses depending on form alone	14	(87½%)
No. of responses depending on color	2	(12½%)

Content of the responses:

Animals	10	(62½%)
Human beings	1	(6%)
Objects	3	(19%)
Nature	2	(12½%)

The average number of responses determined by form alone do not normally exceed 50 per cent of the total number of interpretations. The fact that this boy relies so heavily on form denotes a severe repression of any type of experience other than the most controlled formal one. On the two occasions when he does introduce color the responses burst forth in wild, uncontrolled fashion, both answers consisting of "fire, burning up everything." It is evident that his exaggerated control has been employed to keep his aggressive impulses in check. The absence of movement answers indicates that he cannot deal with these on a fantasy level, and that if they ever gain the upper hand they will precipitate him into unacceptable behavior. He therefore tries in the only way at his disposal to deal with his problems, but it is apparent from his outbursts that his control cannot always be maintained. Furthermore, the very low number of whole responses given indicates a lack of drive toward achievement. The constrictive

control this boy is employing in his adjustive efforts has had repercussions in his mental functioning, curtailing his mental energy. This would account to a considerable extent for his present school failure. The curtailment apparent in his emotional and intellectual life is also evident in the fact that he shows a relatively limited range of interests (only four categories listed under content of responses). This boy needs help in developing other methods of handling his impulses, possibly dramatics, wrestling, etc., so that he need not strive for the rigid control which he manifests at present and which is interfering with his development and adjustment.

THEMATIC APPERCEPTION TEST

The Thematic Apperception Test was devised by Murray and his associates at the psychology laboratory of Harvard University. It consists of thirty pictures somewhat like those used to illustrate magazine stories. Some of the pictures are intended primarily for men, some for boys, some for women, some for girls, and others for everyone. Murray's original instructions were to give the test in two parts, presenting ten pictures at one session and ten at a later session. Most examiners now use just ten pictures and complete the examination in one sitting.

As with the Rorschach, the instructions are simple. The subject is told that he is to be shown some pictures and he is to make up a story for each one. He is to tell what led up to the event, what is happening at the moment, what the characters are feeling and thinking, and what the outcome will be. The exact wording is modified to meet the intellectual level of the subject.

Here again, the situation is left to the subject. His story may be happy or sad, bloodthirsty or peaceful, his characters may be doing anything he wants them to do, the outcomes may be cheerful or mournful, successful or unsuccessful. Characters may be introduced and those in the picture neglected.

It is assumed that the child identifies with the "hero" or central figure in the story. The way this figure is described, the forces brought to bear on him and the way he handles his problems are reflections of the subject's own feelings and attitudes. Such an assumption is logical in view of the fact that it is patently impossible to create something, even a story, unless one has identified to some extent with the characters and events involved in the story. This is a basic principle underlying all creative activity.

The stories which the subject tells are analyzed in terms of (1) the types of individual the subject identifies with, that is, does he see the hero as happy, defeated, rejected, and so on; (2) the needs this hero manifests; (3) the environmental forces with which the hero must contend; (4) the interaction between the hero's needs and external pressures; (5) the nature of the outcome, that is, does the hero find what he seeks, is he successful, or does he suffer frustration and defeat? The frequency of positive and negative outcomes and the factors that occasion them, such as the presence of the father, for example, whenever things go wrong; the consistency of any special needs, as for example, the need for power, for love, for punishment; the nature of the environmental forces with which the hero contends, namely,

authority, economic deprivation, and others, are all calculated and correlated with one another.

CASE 2.—A boy 7 years, 11 months of age, with an intelligence quotient of 147, was considered by his mother to be an unhappy child. He was difficult to live with because of his emotional outbursts and his unpredictable behavior. At times he was unusually good and mature, at other times most infantile and disobedient.

The stories which he gave on the Thematic Apperception Test in almost every instance indicated his identification with a child who "didn't look where he was going," "who ran into things," "the mother always watched him," and similar concepts. In spite of the mother's protests that she did not nag him, it is obvious that, from the child's point of view, he is always in difficulties and never able to please those about him. He is therefore convinced that he is not acceptable to her, otherwise she would not be constantly trying to change him. Yet it is also evident that he goes out of his way to draw her reproaches onto himself. There seems to be a need for attention of this negative order and his stories further suggest that this alleviates his feelings of guilt which arise from his aggression toward his mother and the death wishes he has against his brother. This guilt is apparently somewhat appeased when he is exposed to maternal harshness and so this need compels him to do things he knows are displeasing and will bring him punishment.

CHILDREN'S APPERCEPTION TEST

Because children identify more readily with animals than with adults, Bellak has developed what he calls the Children's Apperception Test for 3- to 10-year-old subjects. The test consists of ten pictures of animals engaged in activities which are important for this group. One picture represents baby chicks eating with the mother chick hovering in the background; another includes a toilet training scene (Fig. 2), another a rabbit alone in a crib in a dark room. These pictures are more appropriate for the child than are most of the Thematic Apperception Test pictures, and the child is generally more willing to reveal his problems as though they were the problems of the animal than to talk about them in connection with human figures.

Fig. 2.—(From Bellak, L., and Bellak, S. S.: J. Projective Techniques, p. 173, 1950.)

CASE 3.—A 7-year-old boy of average intelligence was referred because of frequent intestinal upsets for which there was no ascertainable physical cause. All his stories dealt with food, even when the pictures did not lend themselves to such treatment. For example, in the case of the rabbit in the dark room he went into a long description of the mother's activities in the kitchen where she was preparing the rabbit's meals for the next day. Such emphasis suggested that this child was suffering from strong feelings of emotional deprivation associated with tension and anxiety which could account for his intestinal upheavals. His history revealed that he was being cared for by his maternal grandmother and an uncle. The mother had deserted when he was an infant, and the father was an unstable individual who wandered about the country going from one job to another. He was practi-

cally a stranger to the patient. Recently the father had remarried and wanted to take the son into his new home. The child had heard of the plans that were being made for him and was greatly distressed at the thought of losing the only security and mother love he had ever known.

DISCUSSION

In examining a child it is customary to give a number of tests rather than just one. Among these are generally an intelligence test, possibly school achievement tests, drawings of human figures, and one or more of the projective tests. The use of several tests is important since each one gives different information about the personality of the child, highlights different facets of behavior, and probes different levels of the personality. Thus, the intelligence test gives a picture of the child's intellectual strengths and weaknesses. The Rorschach, on the other hand, points up the degree of emotional control he has attained, the effect of his emotional reactions on his intellectual functioning, the personality resources at his disposal, and the use he is making of them. The apperception tests reveal the sources of the child's specific disturbances. Sometimes the quality of the productions on the Rorschach or the Children's Apperception Test indicates that the child's potentialities are much better than his formal I.Q. suggests, but that because of his emotional difficulties he is not applying his assets fully and constructively. Conversely, there are those who can perform with considerable efficiency when tasks are laid out and planned for them as on the intelligence test but who become strikingly inadequate when called on to organize things on their own. Knowing such facts about a child can be helpful in deciding how a child's problem can be best handled, the need for psychotherapy as against a "let well enough alone" policy, the type of school he should attend, and so on.

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Comments on Current Literature

SACROCOCCYGEAL TERATOMAS

THE Boston Children's Hospital Staff reports its long-term experience dealing with sacrococcygeal teratomas in the March, 1951, issue of *Surgery, Gynecology and Obstetrics* in a collaboration by Drs. Robert E. Gross, H. William Clatworthy, Jr., and Irving A. Meeker, Jr. Their review of a thirty-year period ending May 1, 1950, involves the study of forty patients with sacrococcygeal teratoma, twenty-eight of whom were treated within the last ten years.

Teratomas, which are defined as composite masses possessing more than one germinal layer, appear most commonly in infants and children in the sacrococcygeal area. Teratomas in this region are most commonly observed at birth or shortly thereafter, and are found to be much more common in females than in males. Although the majority of sacrococcygeal tumors of this type remain benign, a significant percentage of them become malignant. In the Boston Children's series, eleven of the forty cases studied exhibited histologically malignant characteristics. Pathologically it was important that many of the benign tumor masses with no evidence of malignant change were observed to spread anterosuperiorly into the hollow of the sacrum, displacing and distorting regional organs but actually not invading them. Despite this tendency for local extension, even large masses of this type could be shelled out completely without injury to adjacent viscera. This unique feature of benign sacrococcygeal teratomas permitted surgical dissection and complete removal of unusually large masses which seemed to be encroaching on important vital organs. Of further importance surgically was the observation that sacrococcygeal teratomas usually are attached to the coccyx, and that removal of the entire coccyx must be carried out if the surgeon is striving for complete eradication of the tumor mass.

The authors report that thirty-two of their forty patients were females, thus verifying the general impression in the literature that sacrococcygeal teratomas are decidedly more common in the female sex. Thirty-two of their forty cases were diagnosed in the newborn period, detected by an easily recognizable externally protruding lump. The remaining eight cases in their series were discovered in subjects who had reached ages varying from 4 months to 5 years. These tumor masses, when first recognized after the newborn period, were characteristically small and deep-seated and showed much less in the way of an external mass. In differentiating teratomas from other masses which may appear in the sacrococcygeal region, particularly meningoceles and myelomeningoceles, it was of diagnostic importance that in no patient with sacrococcygeal teratoma was a neurological defect demonstrated in the extremities or in the sphincteric mechanism of bladder or rectum.

On the basis of their extensive surgical and pathological experience, Gross and his associates advocate emphatically that every patient with a sacrococcygeal teratoma should be offered the benefit of surgery regardless "of the large size of the mass or the small size of the patient." Since evidence of metastasis could be demonstrated in very few cases, radical excision of the sacrococcygeal mass was justified in the vast majority of patients.

The results are summarized as follows. Of the forty in the series, two

patients died before surgery could be undertaken; four patients had distant metastases and were subjected to biopsy only; three patients who had been operated upon in other clinics and had recurrences were subjected to a second operation and are now apparently well. In only one instance the parents refused surgery. The remaining thirty patients were treated initially by the Boston group, and operative removal of the teratoma was carried out in each instance. Of this group, there were seven local recurrences of the tumor occurring from nine months to three years after surgery. In one instance a tiny residual calcified mass was noted in front of the sacrum. This mass has been known to be present for fifteen years, and the patient refuses further surgery. A second patient in this group developed pulmonary metastases and died. The remaining patients with recurrences were subjected to a second operation. Of these, three are apparently cured, and two have died of metastases. In the entire series there was only one postoperative death. This newborn infant developed diarrhea on the third day following operation and died on the fourth day.

Final analysis reveals that twenty-nine of the forty patients in the series are now apparently free of tumor. A striking difference is revealed in survival rate between the younger and the older age group. In the newborn group (thirty-two patients) there was surgical treatment of twenty-nine, of whom twenty-six are alive at the present time, presumably cured. Of the eight patients in the older group (4 months to 5 years of age) three have survived and are apparently free of their disease.

Comprehensive reports of this caliber re-emphasize the great value of records carefully kept over long periods of time, and demonstrate again the significant contributions which may result from thoughtful collaboration between the pathologist and the clinician.

RUSSELL J. BLATTNER

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Cincinnati, Ohio, March 30, 31, and April 1, 1951.

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A Pediatric Conference will be held by the **University of California School of Medicine** June 18 through 22, 1951. Dr. Larson Wilkins, of Johns Hopkins University, will be the guest lecturer.

Book Reviews

The Pharmacological Basis of Penicillin Therapy. Karl H. Beyer, Springfield, Ill., 1950, Charles C Thomas, 214 pages. Price $4.50.

This monograph presents briefly the pharmacological basis of penicillin therapy and claims to be the first review summarizing this broad field. It will be of interest to clinicians, medical students, and pharmacologists. The material is well organized to serve as a practical reference for the busy reader. A concise summary heads each of the seven chapters, promoting accessibility of discussion and of the data which some fifty figures and tables set forth. Treatment has been kept within the general appreciation of the average medical student. In Chapters I and II is summarized much of the basic pharmacology pertaining to the absorption, distribution, and inactivation of penicillin. Chapter III is devoted to a discussion of the mode of action of penicillin in sufficient detail to serve as a basis for the presentation of the two current philosophies of dosage regime in therapy, while Chapter IV considers repository forms of penicillin products. The remaining three chapters deal with the renal elimination of penicillin and measures that have been developed to suppress reversibly its tubular secretion. Chapter VI in particular describes the enzymological and physiological consideration of the renal tubular secretion of penicillin and its inhibition. Chapter VII reviews the pharmacology and clinical utility of combined caronamide and penicillin therapy. Here are correlated for the first time the enzymological, the renal physiological, and the clinical bases of this new approach to penicillin therapy. In an addendum to the text there is given a description of a more recently developed compound, "Benemid," which may significantly influence oral penicillin therapy. A bibliography of over 400 references, a full general index, clarity of presentation together with the use of large clear type are additional points which combine to make this handy volume one to be desired by those interested in this field.

RUTH B. GERSTUNG

Modern Trends in Pediatrics. Edited by Sir Leonard Parsons, New York, 1951, Paul B. Hoeber, Inc., 600 pages. Price $12.00.

This volume contains a discussion of the trends or developments in twenty-one selected pediatric topics by men regarded as authorities in their respective fields. Most of the authors are from the British Commonwealth—England, Scotland, Ireland, Canada, and Australia. For two discussions the Editor has turned to Sweden, and for one each to Holland and the United States. Almost without exception the authors have done an excellent job and the discussions reach a high level.

It is not a systematic text but a discussion of selected subjects or fields in which there has been striking progress in recent

years. Thus rickets and scurvy, which dominated British contributions in the past, are omitted. It is difficult to select some of the articles for special mention, but this perhaps is the best way to indicate the contents and the scope of the volume. In the opening chapter Dodds of Sydney, Australia, gives an excellent discussion of congenital malformations following rubella and other viral infections. The chapter on the normal development of the infant by Illingworth of Sheffield, although only twenty-five pages in length, is one of the best discussions of this important subject for the student and practitioner we have run across. Chapter 13 on the progress and problems in viral diseases of special importance in childhood by Sabin, of Cincinnati, is outstanding, and gives a clear picture of the present status of this important field. Tuberculosis is adequately presented by Wallgren of Sweden, as is chemotherapy by Gailsford of Manchester. Crooke, of Birmingham, has an excellent discussion of endocrinology, and van Creveld, of Holland, discusses the complex subject of the lipoidoses. The discussion of the chondrodystrophies by Neale, of Bristol, is among the best in the book. Keith, of Toronto, contributes the chapter on congenital heart disease, and Sandblom, of Sweden, the discussion of cardio-vascular surgery. The discussions are well written, amply illustrated, and each has an excellent, if brief, bibliography appended.

To those interested in pediatric education, the two chapters by Craig, of Leeds, on "Preventive Pediatric Services," and Moncrief, of London, on the place of "Child Health Institutes in Medical Education and Research" will be of interest. They show the tremendous changes that have taken place in pediatrics in the United Kingdom in recent years, and amply document the statement of Parsons in his preface that pediatrics "has advanced in the last few years from a rather insignificant and certainly neglected section of medicine to become one of the major subjects of the medical curriculum." It is the same change that pediatrics underwent some thirty years ago in the United States.

One cannot but wish, on reading the volume, that Sir Leonard Parsons had lived to see the publication of this volume which he fathered, and received the praise which it merits. He was the leader in many ways of this rebirth of pediatrics in the United Kingdom. Although he modestly has not contributed a chapter, which he might well have done, this group of essays which he edited is a fine tribute to the man and his work. In this sense it turns out to be a splendid memorial to a man who was an outstanding international leader in pediatrics, and a gentleman who was respected by his colleagues throughout the world. While the volume is concerned with the discussion of trends in specific fields, as the Editor aptly remarks in his preface, the recognition of the importance of the subject is the outstanding modern trend in pediatrics in the United Kingdom. Certainly no one had more to do with this "modern trend" than Sir Leonard Parsons.

B. S. V.

Pediatric X-ray Diagnosis, John Caffey, A.B., M.D., ed. 2., Chicago, 1950, The Year Book Publishers, Inc., 862 pages, 1039 illustrations. Price $22.50.

Since the publication of the first edition of Caffey's *Pediatric X-ray Diagnosis* five years ago, it has become a standard authoritative work of reference for pediatricians and roentgenologists. The general form of presentation has been retained, but a great deal has been rewritten and added, including some 385 new figures. Among some twenty-odd new subjects are external deformities of the thoracic wall, fetal aspiration, meconium peritonitis, Pyle's and Engelmann's diseases, and the Ellis-Creveld syndrome.

A number of sections have been enlarged, as those on congenital malformation of the heart, megacolon, and primary pulmonary tuberculosis. Many new references to the literature have been added. The plates are clear and the book is printed on good paper. The high cost reflects the tremendous increase in the cost of printing and paper stock during the last four or five years. Despite the cost, the book is literally a "must" for the pediatrician who wishes to keep abreast of modern pediatric diagnosis, as it is unique in its field.

Editor's Column

PARALYTIC POLIOMYELITIS FOLLOWING IMMUNIZING INJECTIONS

DURING the past year a number of British and Australian investigators have observed a relation between poliomyelitis and immunizing injections against diphtheria and/or pertussis given within a month of the onset of paralysis.[1, 2, 3, 4, 5, 6] Not only was a correlation reported between the localization of paralysis and the site of previous inoculation but in a number of cases the paralysis was either limited to or was most severe in the inoculated limb. Most of the authors found no evidence that injections given over a month before onset bore any relation to either the incidence or localization of paralysis.

In a carefully controlled study of the Minnesota outbreak in 1946 Anderson and Skaar[7] have confirmed the British and Australian observations. The American investigators found that in patients with paralytic poliomyelitis who had been immunized during the month prior to onset there was a close correlation between site of paralysis and site of injection. The evidence was as follows: thirty-three patients in whom paralysis developed within one month after inoculation were compared with fifty-two patients in whom paralysis appeared two to six months after inoculation. The incidence of "correlated cases" (those showing paralysis of the inoculated extremity) was 19/33 (58 per cent) in the "one month" group and 8/52 (15 per cent) in the "two- to six-month" group. The distribution of paralysis, furthermore, was different in the two groups, especially when the patients under 2 years of age were considered. Paralysis of the arm was more likely to occur in those inoculated within one month of onset than in those comprising the "two- to six-month" group, the incidence being 14/19 (74 per cent) and 4/19 (21 per cent), respectively. Of the nineteen correlated "one-month" cases, seven patients showed paralysis only of the inoculated limb, seven others had frank paralysis in the inoculated limb but some weakness in other parts of the body, while five showed additional definite paralysis in some other region. There was a definite trend toward more severe involvement of the injected extremity. The authors point out that these data, although derived from small numbers, are in exact harmony with the British reports.

Although the findings of McCloskey[2] in Australia and of Geffen[3] in England suggested that pertussis antigen was especially implicated, the report of Anderson and Skaar failed to indicate that the relationship is associated with any one antigen.

The studies of Korns, Albrecht, and Locke,[8] based on over 2,000 cases in New York State in 1950, indicate a relationship not only with immunizations but with penicillin injections and various other injections, that is, of vitamins, hormones, sedatives, and Novocain for dental work. There were seven cases of paralysis in the last group, six of them bulbar.

The conclusion is inescapable that immunization and other types of injections within four weeks of onset somehow condition the ensuing paralysis. Just how this is brought about remains a mystery. It seems unlikely that the

various antigens or other materials were contaminated with poliomyelitis virus. Although the possibility has been raised of virus on the skin being carried in with the needle, as yet no virus has been detected on the skin despite vigorous searches in the handwashings of patients and family contacts.[9] A third theoretical explanation holds that the inoculum affects the tissues in a fashion analogous to excessive fatigue which is known to predispose to paralysis.

At all events, the present evidence seems clear enough to warrant the postponement of immunizations and other elective inoculations during the summer and fall months when poliomyelitis is likely to appear in epidemic form.

R. W.

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INDEX TO VOLUME 38

AUTHORS INDEX*

A

ADAMS, FORREST H., VEASY, L. GEORGE, JORGENS, JOSEPH, DIEHL, ANTONI, LABREE, JOHN W., SHAPIRO, M. J., AND DWAN, PAUL F., Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

ALDERSON, LEE R. (WITH BARMEYER, GEORGE H., AND COX, WALTER B.), Traumatic periostitis in young children, 184

ALPERN, E. BRYCE (WITH LYNCH, JOHN F.), Results of histoplasmin skin testing in children from the St. Louis, Mo., area, 51

AMATRUDA, CATHERINE S., AND BALDWIN, JOSEPH V., Current adoption practices, 208

ANDERSON, O. WILLIAM, The management of "infantile insomnia," 394

ASH, RACHEL (WITH FRIEDMAN, SIDNEY, AND MURPHY, LOIS), Aortic atresia with hypoplasia of the left heart and aortic arch, 354

ASHE, ROSEMARY (WITH EPSTEIN, HAROLD C., AND HOCHWALD, ADOLF), Salmonella infections of the newborn infant, 723

B

BALDWIN, JOSEPH V. (WITH AMATRUDA, CATHERINE S.), Current adoption practices, 208

BARMEYER, GEORGE H., ALDERSON, LEE R., AND COX, WALTER B., Traumatic periostitis in young children, 184

BECK, CLAUDE S. (WITH KINLEY, GORDON, AND RILEY, HARRIS D.), Subdural hematoma, hygroma, and hydroma in infants, 667

BINNS, VERONICA B. (WITH PRICE, WALTER C.), A treatment program for chronic childhood sinobronchitis, 597

BLATTNER, RUSSELL J., Congenital damage of the nervous system by an arthropod-borne encephalitis virus, 402

—, Infectious mononucleosis, 267

—, Polymyxin in the treatment of meningitis due to Pseudomonas aeruginosa, 530

—, Retrolental fibroplasia, 661

—, Sacrococcygeal teratomas, 776

—, Vesicular stomatitis virus of cattle producing human disease, 141

BLOCH, HARRY, WALDRON, ROBERT J., AND COGAN, GILBERT M., Sickle-cell disease: report of a case with anemia, subarachnoid hemorrhage and cerebral thrombosis, 88

BLOXSOM, ALLAN, A self-lubricating syringe, 491

—, The function of a recovery nursery in a large maternity hospital, 618

BOOHER, CRAIG E., FARRELL, JAMES B., AND WEST, EDWARD J., Pertussis: clinical comparison of the newer antibiotics, 411

BOROVSKY, MAXWELL P. (WITH KADISON, ELMER R.), The treatment of infantile diarrhea with a new combination of antibiotics, 576

BOYD, HOWARD, AND HELFRICK, FRANCIS, Celiac disease treated with polyoxyethylene sorbitan monooleate, 493

BRADLEY, J. EDMUND, PROUTT, LEAH, SHIPLEY, E. RODERICK, AND OSTER, ROBERT H., An evaluation of a carbohydrate-phosphoric acid solution in the management of vomiting, 41

BRITTEN, SIDNEY A. (WITH RUBENSTEIN, A. DANIEL), Epidemic diarrhea of infancy, 457

BROWN, THELMA G. (WITH LOWREY, GEORGE H.), Precocious sexual development, 325

BURDICK, WILLIAM FOSTER (WITH FERIOZI, DAN, RICE, E. CLARENCE, AND TROENDLE, FRANCIS J.), Thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction in infancy, 235

C

CAMPBELL, MEREDITH, Urologic considerations in pediatrics, 387

CAPLAN, HYMAN, Some interview techniques in child psychiatry, 128

CARITHERS, HUGH A., Mother-pediatrician relationship in the neonatal period, 654

CASAMAJOR, LOUIS, LAIDLAW, ROBERT W., AND KOZINN, PHILIP J., The technique of pneumoencephalography in children: comparative results with air and oxygen injection, 463

CERMAK, ETHEL G. (WITH WINKLEY, RUTH, JACKSON, KATHERINE, FAUST, OTTO A., AND MURRAY, MARJORIE F.), Emotional reactions and behavior of children in the home, 476

*January, pp. 1-146; February, pp. 147-274; March, pp. 275-410; April, pp. 411-536; May, pp. 537-666; June, pp. 667-782.

CHAMPLIN, GARDNER (WITH TRAISMAN, HOWARD S.), Salmonella typhimurium osteomyelitis, 244

CHANG, S. Y., AND SU, T. F., Clinical evaluation of streptomycin in the treatment of bacillary dysentery in infancy and childhood, 602

CHILD, CHARLES G., III (WITH O'SULLIVAN, WARD D.), Ileocecal intussusception caused by lymphoid hyperplasia, 320

CLATWORTHY, H. WILLIAM, JR. (WITH GROSS, ROBERT E.), Twin fetuses in fetu, 502

COFFEE, J. Y. (WITH MCCULLOUGH, G. C., TRICE, P. A., JR., STONE, J. J., AND CRANDALL, H. L.), Acute glomerulonephritis: impetigo as an etiological factor, 346

COGAN, GILBERT M. (WITH BLOCH, HARRY, AND WALDRON, ROBERT J.), Sickle-cell disease: report of a case with anemia, subarachnoid hemorrhage, and cerebral thrombosis, 88

COHEN, PHILIP, SCHNECK, HERMAN, AND DUBOW, EMANUEL, Prenatal multiple immunization, 696

COHEN, SHELDON G., Penicillin sensitivity simulating atopic dermatitis, 741

COOK, C. D. (WITH SHWACHMAN, H., AND FOLEY, G. E.), Aureomycin in pediatrics: a review, 91

COX, WALTER B. (WITH BARMEYER, GEORGE H., AND ALDERSON, LEE R.), Traumatic periostitis in young children, 184

CRANDALL, H. L. (WITH MCCULLOUGH, G. C., COFFEE, J. Y., TRICE, P. A., JR., AND STONE, J. J.), Acute glomerulonephritis: impetigo as an etiological factor, 346

CRUMP, E. PERRY (WITH TANNER-CAIN, NATALIA), Situs inversus, 199

CUNNINGHAM, GUY C., AND HARLEY, JOHN F., A case of Turner's syndrome, 738

CURNEN, EDWARD C. (WITH RABE, EDWARD F.), The occurrence of lysozyme in the cerebrospinal fluid and serum of infants and children, 147

D

DAESCHNER, C. WILLIAM, DEISHER, ROBERT W., AND HARTMANN, ALEXIS F., Later status of juvenile diabetics, 8

DAVISON, WILBURT C., Correspondence, 663

DEAN, G. O. (WITH EARLE, A. M., AND REILLY, W. A.), Thymectomy and ACTH in lymphatic leucemia, 63

DEISHER, ROBERT W. (WITH DAESCHNER, C. WILLIAM, AND HARTMANN, ALEXIS F.), Later status of juvenile diabetics, 8

DEKLEINE, E. HOYT (WITH NETER, ERWIN, AND EGAN, RICHARD W.), Treatment with aureomycin of localized Pasteurella multocida infection, 242

DENHOFF, ERIC, AND HOLDEN, RAYMOND H., The significance of delayed development in the diagnosis of cerebral palsy, 452

— (WITH LAUFER, MAURICE W., GIUNTA, FRANK, TRAMONTI, DANIEL V., AND HARDY, ELEANOR P.), Clinical study in man of the effects of variation of agenized flour products in the diet, 341

DENTON, FLORENCE (WITH HAZARD, SPRAGUE, AND SMITH, CLEMENT A.), A clinical study concerning the value of Biolac. III. Effect of changes introduced in New Improved Biolac upon growth of young infants, 18

DESANCTIS, ADOLPH G. (WITH SOUTHARD, SAMUEL C., AND WALDRON, ROBERT J.), Hemangioma associated with thrombocytopenic purpura, 732

DIEHL, ANTONI (WITH ADAMS, FORREST H., VEASY, L. GEORGE, JORGENS, JOSEPH, LABREE, JOHN W., SHAPIRO, M. J., AND DWAN, PAUL F.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

DIGEORGE, ANGELO, AND NELSON, WALDO E., Some observations on the use of adrenocorticotropic hormone in atopic dermatitis in infancy, 164

DUBOW, EMANUEL (WITH COHEN, PHILIP, AND SCHNECK, HERMAN), Prenatal multiple immunization, 696

DWAN, PAUL F. (WITH ADAMS, FORREST H., VEASY, L. GEORGE, JORGENS, JOSEPH, DIEHL, ANTONI, LABREE, JOHN W., AND SHAPIRO, M. J.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

E

EARLE, A. M., REILLY, W. A., AND DEAN, G. O., Thymectomy and ACTH in lymphatic leucemia, 63

— (WITH REILLY, W. A.), Treatment of typhoid fever with terramycin, 428

EGAN, RICHARD W. (WITH NETER, ERWIN, AND DEKLEINE, E. HOYT), Treatment with aureomycin of localized Pasteurella multocida infection, 242

ELLINGSON, R. J., Major hereditary ectodermal dysplasia, 191

EPSTEIN, HAROLD C., HOCHWALD, ADOLF, AND ASHE, ROSEMARY, Salmonella infections of the newborn infant, 723

ETTELDORF, JAMES N., Methylene blue in the treatment of methemoglobinemia in premature infants caused by marking ink, 24

EXLINE, A. L., JR., AND HARRINGTON, M. R., Retrolental fibroplasia: clinical statistics from the premature center of the Charity Hospital of Louisiana at New Orleans, 1

F

FARRELL, JAMES B. (WITH BOOHER, CRAIG E., AND WEST, EDWARD J.), Pertussis: clinical comparison of the newer antibiotics, 411

FAUST, OTTO A. (WITH WINKLEY, RUTH, JACKSON, KATHERINE, MURRAY, MARJORIE F., AND CERMAK, ETHEL G.), Emotional reactions and behavior of children in the home, 476

FELDMAN, SAMUEL, GOODGOLD, JOSEPH, LEVY, HAROLD, AND ZALEZNAK, BERNARD D., Acute thrombosis of the femoral artery in an infant, 498

FERIOZI, DAN, RICE, E. CLARENCE, BURDICK, WILLIAM FOSTER, AND TROENDLE, FRANCIS J., Thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction in infancy, 235

FOLEY, G. E. (WITH SHWACHMAN, H., AND COOK, C. D.), Aureomycin in pediatrics: a review, 91

FORBES, GILBERT B., AND PERLEY, ANNE M., Treatment of hyperthyroidism with radioactive iodine, 158

— (WITH PERLEY, ANNE, AND PENNOYER, MIRIAM M.), Determination of sodium^{24} "space" in infants, children, and adults, 299

FORSYTH, CONSTANCE C. (WITH KEITH, JOHN D.), Auricular septal defects in children, 172

FREUD, PAUL, Evolution of systemic reticuloendotheliosis in childhood, 744

FRIEDMAN, SIDNEY, MURPHY, LOIS, AND ASH, RACHEL, Aortic atresia with hypoplasia of the left heart and aortic arch, 354

FURMAN, ROBERT A., HELLERSTEIN, HERMAN K., AND STARTZMAN, VIOLA V., Electrocardiographic changes occurring during the course of replacement transfusions, 45

G

GILLESPIE, JAMES B., AND MUSSEY, ROBERT D., Progressive diaphyseal dysplasia (Engelmann's disease), 55

GIUNTA, FRANK (WITH LAUFER, MAURICE W., DENHOFF, ERIC, TRAMONTI, DANIEL V., AND HARDY, ELEANOR P.), Clinical study in man of the effects of variation of agenized flour products in the diet, 341

GOLDIN, MILTON (WITH PADNOS, EMANUEL), Salmonella bareilly meningitis in a child successfully treated with intravenous aureomycin, 85

GOLDRING, DAVID, Neuroblastoma sympathetic um with metastases, 231

GOLDSTEIN, EUGENE O. (WITH HARDY, JANET B.), The feeding of premature infants: the value of high caloric diets in reducing the length of hospital stay, 154

GOLDWYN, ARTHUR, An unusual anomaly of the aortic arch, 442

GOODGOLD, JOSEPH (WITH FELDMAN, SAMUEL, LEVY, HAROLD, AND ZALEZNAK, BERNARD D.), Acute thrombosis of the femoral artery in an infant, 498

GREENBERG, MORRIS (WITH SIEGEL, MORRIS, AND MAGEE, M. CATHERINE), Tonsillectomy and poliomyelitis. I. Studies on incidence in 1949, 537

— (WITH — AND —), Tonsillectomy and poliomyelitis. II. Frequency of bulbar paralysis, 1944-1949, 548

GROSS, ROBERT E., AND CLATWORTHY, H. WILLIAM, JR., Twin fetuses in fetu, 502

GRUBER, SEYMOUR (WITH STERNBERG, S. DAVID, ZWEIFLER, BEN M., AND LICHTERMAN, JACOB), The Shwartzman phenomenon complicating acute meningococcemia with meningitis, 369

H

HALPERN, FLORENCE, Projective tests in the personality investigation of children, 770

HARDY, ELEANOR P. (WITH LAUFER, MAURICE W., DENHOFF, ERIC, GIUNTA, FRANK, AND TRAMONTI, DANIEL V.), Clinical study in man of the effects of variation of agenized flour products in the diet, 341

HARDY, JANET B., AND GOLDSTEIN, EUGENE O., The feeding of premature infants: the value of high caloric diets in reducing the length of hospital stay, 154

HARLEY, JOHN F. (WITH CUNNINGHAM, GUY C.), A case of Turner's syndrome, 738

HARRINGTON, M. R. (WITH EXLINE, A L., JR.), Retrolental fibroplasia: clinical statistics from the premature center of the Charity Hospital of Louisiana at New Orleans, 1

HARTENSTEIN, HANS (WITH LEVINSON, ABRAHAM), Intracranial calcification following pneumococcic meningitis, 624

HARTMAN, EVELYN E., AND KENNEDY, ROGER L. J., Illness in the first trimester of pregnancy: its lack of significance in relation to congenital anomaly of the offspring and to full-term pregnancy, prematurity, and stillbirth, 306

HARTMANN, ALEXIS F. (WITH DAESCHNER, C. WILLIAM, AND DEISHER, ROBERT W.), Later status of juvenile diabetics, 8

HAWKINS, RICHARD D., A new suckling device for artificial infant feeding, 484

HAZARD, SPRAGUE, SMITH, CLEMENT A., AND DENTON, FLORENCE, A clinical study concerning the value of Biolac. III. Effect of changes introduced in New Improved Biolac upon growth of young infants, 18

HELFRICK, FRANCIS (WITH BOYD, HOWARD), Celiac disease treated with polyoxyethylene sorbitan monooleate, 493

HELLERSTEIN, HERMAN K. (WITH FURMAN, ROBERT A., AND STARTZMAN, VIOLA V.), Electrocardiographic changes occurring during the course of replacement transfusions, 45

HELMSWORTH, JAMES A., AND PRYLES, CHARLES V., Congenital tracheoesophageal fistula without esophageal atresia, 610

HIGH, ROBERT H., AND REINER, CHARLES B., Ineffectiveness of aureomycin in preventing the primary vaccinia reaction, 60

HOCHWALD, ADOLF (WITH EPSTEIN, HAROLD C., AND ASHE, ROSEMARY), Salmonella infections of the newborn infant, 723

HOFFMAN, CHARLES (WITH STERNBERG, S. DAVID, AND ZWEIFLER, BEN M.), Stomatitis and diarrhea in infants caused by Bacillus mucosus capsulatus, 509

HOLDEN, RAYMOND H. (WITH DENHOFF, ERIC), The significance of delayed development in the diagnosis of cerebral palsy, 452

HOLLIDAY, POPE B., JR. (WITH STARR, HAROLD J.), Erythema multiforme as a manifestation of neonatal septicemia, 315

HOWARD, ANN (WITH JOSLIN, BLACKBURN S.), Hemophilus influenzae pyarthrosis and meningitis treated with aureomycin, 375

J

JACKSON, IRA J., A review of the surgical treatment of internal hydrocephalus, 251

JACKSON, KATHERINE (WITH WINKLEY, RUTH, FAUST, OTTO A., MURRAY, MARJORIE F., AND CERMAK, ETHEL G.), Emotional reactions and behavior of children in the home, 476

JACOBZINER, HAROLD, The Astoria Plan: a decade of progress, 221

JENKINS, SAMUEL (WITH WRIGHT, LYDIA), Erythema multiforme exudativum, 310

JOHNSON, ALEXANDER C., AND MEREDITH, JOHN M., Suprasellar (Rathke's pouch) cyst, 380

JOHNSON, ELOISE EBERLING, WARNER, MARY, AND SIMONDS, J. P., Total absence of the cerebral hemispheres, 69

JORGENS, JOSEPH (WITH ADAMS, FORREST H., VEASY, L. GEORGE, DIEHL, ANTONI, LABREE, JOHN W., SHAPIRO, M. J., AND DWAN, PAUL F.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

JOSLIN, BLACKBURN S., AND HOWARD, ANN, Hemophilus influenza pyarthrosis and meningitis treated with aureomycin, 375

K

KADISON, ELMER R., AND BOROVSKY, MAXWELL, P. The treatment of infantile diarrhea with a new combination of antibiotics, 576

KALLET, HERBERT I. (WITH NICHAMIN, SAMUEL J.), Anomalous anal papillae in infants and children, 468

KAUFMAN, BENJAMIN, LEVY, HAROLD, ZALEZNAK, BERNARD D., AND LITVAK, ABRAHAM M., Statistical analysis of 242 cases of meningococcus meningitis, 705

KEITH, JOHN D., AND FORSYTH, CONSTANCE C., Auricular septal defects in children, 172

KELLY, JAMES J., AND SHAFFER, JAMES G., Hemolytic disease of the newborn in dizygotic twins: an interesting family history, 717

KENNEDY, ROGER L. J. (WITH HARTMAN, EVELYN E.), Illness in the first trimester of pregnancy: its lack of significance in relation to congenital anomaly of the offspring and to full-term pregnancy, prematurity, and stillbirth, 306

KINLEY, GORDON, RILEY, HARRIS D., AND BECK, CLAUDE S., Subdural hematoma, hygroma, and hydroma in infants, 667

KOZINN, PHILIP J. (WITH CASAMAJOR, LOUIS, AND LAIDLAW, ROBERT W.), The technique of pneumoencephalography in children: comparative results with air and oxygen injection, 463

L

LAIDLAW, ROBERT W. (WITH CASAMAJOR, LOUIS, AND KOZINN, PHILIP J.), The technique of pneumoencephalography in children: comparative results with air and oxygen injection, 463

LAUFER, MAURICE W., DENHOFF, ERIC, AND GIUNTA, FRANK, WITH TECHNICAL ASSISTANCE OF TRAMONTI, DANIEL V., AND HARDY, ELEANOR P., Clinical study in man of the effects of variation of agenized flour products in the diet, 341

LaBree, John W. (with Adams, Forrest H., Veasy, L. George, Jorgens, Joseph, Diehl, Antoni, Shapiro, M. J., and Dwan, Paul F.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

Levine, Milton I., A modern concept of breast feeding, 472

Levinson, Abraham, and Hartenstein, Hans, Intracranial calcification following pneumococcic meningitis, 624

Levy, Harold (with Feldman, Samuel, Goodgold, Joseph, and Zaleznak, Bernard D.), Acute thrombosis of the femoral artery in an infant, 498

— (with Kaufman, Benjamin, Zaleznak, Bernard D., and Litvak, Abraham M.), Statistical analysis of 242 cases of meningococcus meningitis, 705

Lichterman, Jacob (with Sternberg, S. David, Zweifler, Ben M., and Gruber, Seymour), The Shwartzman phenomenon complicating acute meningococcemia with meningitis, 369

Litvak, Abraham M. (with Kaufman, Benjamin, Levy, Harold, and Zaleznak, Bernard D.), Statistical analysis of 242 cases of meningococcus meningitis, 705

Livingston, Samuel, Abdominal pain as a manifestation of epilepsy (abdominal epilepsy) in children, 687

Lott, George M., The prevention of neuroses, 259

Lowrey, George H., and Brown, Thelma G., Precocious sexual development, 325

Lynch, John F., and Alpern, E. Bryce, Results of histoplasmin skin testing in children from the St. Louis, Mo., area, 51

M

Magee, M. Catherine (with Siegel, Morris, and Greenberg, Morris), Tonsillectomy and poliomyelitis. I. Studies on incidence in 1949, 537

— (with — and —), Tonsillectomy and poliomyelitis. II. Frequency of bulbar paralysis, 1944-1949, 548

McCullough, G. C., Coffee, J. Y., Trice, P. A., Jr., Stone, J. J., and Crandall, H. L., Acute glomerulonephritis: impetigo as an etiological factor, 346

Mercer, Mary E., The pediatrician and his role in understanding children's behavior, 525

Meredith, Howard V., A chart on eruption of the deciduous teeth for the pediatrician's office, 482

Meredith, John M. (with Johnson, Alexander C.), Suprasellar (Rathke's pouch) cyst, 380

Murphy, Lois (with Friedman, Sidney, and Ash, Rachel), Aortic atresia with hypoplasia of the left heart and aortic arch, 354

Murray, Marjorie F. (with Winkley, Ruth, Jackson, Katherine, Faust, Otto A., and Cermak, Ethel G.), Emotional reactions and behavior of children in the home, 476

Mussey, Robert D. (with Gillespie, James B.), Progressive diaphyseal dysplasia (Engelmann's disease), 55

N

Nelson, Waldo E. (with DiGeorge, Angelo), Some observations on the use of adrenocorticotropic hormone in atopic dermatitis in infancy, 164

Neter, Erwin, DeKleine, E. Hoyt, and Egan, Richard W., Treatment with aureomycin of localized Pasteurella multocida infection, 242

Newton, Niles Rumely, The relationship between infant feeding experience and later behavior, 28

Nichamin, Samuel J., and Kallet, Herbert I., Anomalous anal papillae in infants and children, 468

O

Oster, Robert H. (with Bradley, J Edmund, Proutt, Leah, and Shipley, E. Roderick), An evaluation of a carbohydrate-phosphoric acid solution in the management of vomiting, 41

O'Sullivan, Ward D., and Child, Charles G., III, Ileocecal intussusception caused by lymphoid hyperplasia, 320

P

Padnos, Emanuel, and Goldin, Milton, Salmonella bareilly meningitis in a child successfully treated with intravenous aureomycin, 85

Pennoyer, Miriam Mellon, Experiences with an elective rooming-in program, 213

— (with Perley, Anne, and Forbes, Gilbert B.), Determination of sodium^{24} "space" in infants, children, and adults, 299

Perley, Anne, Forbes, Gilbert B., and Pennoyer, Miriam M., Determination of sodium^{24} "space" in infants, children, and adults, 299

— (with Forbes, Gilbert B.), Treatment of hyperthyroidism with radioactive iodine, 158

Poindexter, Hildrus A., A study of the prophylactic value of chloroquine in children, 169

Pomerance, Herbert H., and Salerno, Louis J., A survey of the Rh problem in mixed racial group, 349

PORTER, LANGLEY, A pediatrician looks at psychiatry, 275
PRICE, WALTER C., Sinobronchitis in infants and children, 590
—, AND BINNS, VERONICA B., A treatment program for chronic childhood sinobronchitis, 597
PROUTT, LEAH (WITH BRADLEY, J. EDMUND, SHIPLEY, E. RODERICK, AND OSTER, ROBERT H.), An evaluation of a carbohydrate-phosphoric acid solution in the management of vomiting, 41
PRYLES, CHARLES V. (WITH HELMSWORTH, JAMES A.), Congenital tracheoesophageal fistula without esophageal atresia, 610

R

RABE, EDWARD F., AND CURNEN, EDWARD C., The occurrence of lysozyme in the cerebrospinal fluid and serum of infants and children, 147
REILLY, WILLIAM A., AND EARLE, A. M., Treatment of typhoid fever with terramycin, 428
— (WITH EARLE, A. M., AND DEAN, G. O.), Thymectomy and ACTH in lymphatic leucemia, 63
REINER, CHARLES B. (WITH HIGH, ROBERT H.), Ineffectiveness of aureomycin in preventing the primary vaccinia reaction, 60
RICE, E. CLARENCE (WITH FERIOZI, DAN, BURDICK, WILLIAM FOSTER, AND TROENDLE, FRANCIS J.), Thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction in infancy, 235
RILEY, HARRIS D. (WITH KINLEY, GORDON, AND BECK, CLAUDE S.), Subdural hematoma, hygroma, and hydroma in infants, 667
ROSENBLATT, PHILIP, AND ZWEIFLER, BEN M., Type f Hemophilus influenzae meningitis, 620
RUBENS, ELI, Local hemorrhagic-necrotic skin reaction following penicillin, 630
RUBENSTEIN, A. DANIEL, AND BRITTEN, SIDNEY A., Epidemic diarrhea of infancy, 457

S

SALERNO, LOUIS J. (WITH POMERANCE, HERBERT H.), A survey of the Rh problem in mixed racial group, 349
SCHNECK, HERMAN (WITH COHEN, PHILIP, AND DUBOW, EMANUEL), Prenatal multiple immunization, 696
SCOTT, ROLAND B. (WITH WOODING, CLINTON H.), Terramycin in treatment of pneumonias of childhood, 423
SHAFFER, JAMES G. (WITH KELLY, JAMES J.), Hemolytic disease of the newborn in dizygotic twins: an interesting family history, 717
SHAPIRO, M. J. (WITH ADAMS, FORREST H., VEASY, L. GEORGE, JORGENS, JOSEPH, DIEHL, ANTONI, LABREE, JOHN W., AND DWAN, PAUL F.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431
SHELBY, DONALD C., AND VAUGHN, JOHN O., Juvenile type of Werner's syndrome, 559
SHELOKOV, ALEXIS, AND WEINSTEIN, LOUIS, Poliomyelitis in the early neonatal period: report of a case of possible intrauterine infection, 80
SHIPLEY, E. RODERICK (WITH BRADLEY, J. EDMUND, PROUTT, LEAH, AND OSTER, ROBERT H.), An evaluation of a carbohydrate-phosphoric acid solution in the management of vomiting, 41
SHWACHMAN, H., FOLEY, G. E., AND COOK, C. D., Aureomycin in pediatrics: a review, 91
SIEGEL, MORRIS, GREENBERG, MORRIS, AND MAGEE, M. CATHERINE, Tonsillectomy and poliomyelitis. I. Studies on incidence in 1949, 537
—, —, AND —, Tonsillectomy and poliomyelitis. II. Frequency of bulbar paralysis, 1944-1949, 548
SIMONDS, J. P. (WITH JOHNSON, ELOISE EBERLING, AND WARNER, MARY), Total absence of the cerebral hemispheres, 69
SMITH, CLEMENT A. (WITH HAZARD, SPRAGUE, AND DENTON, FLORENCE), A clinical study concerning the value of Biolac. III. Effect of changes introduced in New Improved Biolac upon growth of young infants, 18
SOBEL, IRWIN PHILIP, AND WILHELM, HAZEL S., The role of the Rh factor in the etiology of cerebral palsy, 447
SOUTHARD, SAMUEL C., DESANCTIS, ADOLPH G., AND WALDRON, ROBERT J., Hemangioma associated with thrombocytopenic purpura, 732
STARR, HAROLD J., AND HOLLIDAY, POPE B., JR., Erythema multiforme as a manifestation of neonatal septicemia, 315
STARTZMAN, VIOLA V. (WITH FURMAN, ROBERT A., AND HELLERSTEIN, HERMAN K.), Electrocardiographic changes occurring during the course of replacement transfusions, 45
STERNBERG, S. DAVID, HOFFMAN, CHARLES, AND ZWEIFLER, BEN M., Stomatitis and diarrhea in infants caused by Bacillus mucosus capsulatus, 509
—, ZWEIFLER, BEN M., GRUBER, SEYMOUR, AND LICHTERMAN, JACOB, The Shwartzman phenomenon complicating acute meningococcemia with meningitis, 369

STONE, J. J. (WITH MCCULLOUGH, G. C., COFFEE, J. Y., TRICE, P. A., JR., AND CRANDALL, H. L.), Acute glomerulonephritis: impetigo as an etiological factor, 346

SU, T. F. (WITH CHANG, S. Y.), Clinical evaluation of streptomycin in the treatment of bacillary dysentery in infancy and childhood, 602

T

TANNER-CAIN, NATALIA, AND CRUMP, E. PERRY, Situs inversus, 199

TRA'SMAN, HOWARD S., AND CHAMPLIN, GARDNER, Salmonella typhimurium osteomyelitis, 244

TRAMONTI, DANIEL V. (WITH LAUFER, MAURICE W., DENHOFF, ERIC, GIUNTA, FRANK, AND HARDY, ELEANOR P.), Clinical study in man of the effects of variation of agenized flour products in the diet, 341

TRICE, P. A., JR. (WITH MCCULLOUGH, G. C., COFFEE, J. Y., STONE, J. J., AND CRANDALL, H. L.), Acute glomerulonephritis: impetigo as an etiological factor, 346

TROENDLE, FRANCIS J. (WITH FERIOZI, DAN, RICE, E. CLARENCE, AND BURDICK, WILLIAM FOSTER), Thrombosis of the inferior vena cava and renal veins with hemorrhagic renal infarction in infancy, 235

V

VAUGHN, JOHN O. (WITH SHELBY, DONALD C.), Juvenile type of Werner's syndrome, 559

VEASY, L. GEORGE (WITH ADAMS, FORREST H., JORGENS, JOSEPH, DIEHL, ANTONI, LABREE, JOHN W., SHAPIRO, M. J., AND DWAN, PAUL F.), Congenital valvular pulmonary stenosis with or without an interatrial communication: physiologic studies as diagnostic aids, 431

W

WALDRON, ROBERT J. (WITH BLOCH, HARRY, AND COGAN, GILBERT M.), Sickle-cell disease: report of a case with anemia, subarachnoid hemorrhage and cerebral thrombosis, 88

WALDRON, ROBERT J. (WITH SOUTHARD, SAMUEL C., AND DESANCTIS, ADOLPH G.), Hemangioma associated with thrombocytopenic purpura, 732

WALKER, A. EARL, The treatment of epilepsy by cortical excision, 285

WARD, ROBERT, Paralytic poliomyelitis following immunizing injections, 781

WARNER, MARY (WITH JOHNSON, ELOISE EBERLING, AND SIMONDS, J. P.), Total absence of the cerebral hemispheres, 69

WEINSTEIN, LOUIS (WITH SHELOKOV, ALEXIS), Poliomyelitis in the early neonatal period: report of a case of possible intrauterine infection, 80

WELSH, JOHN B., The effect of allergy management on growth and development of allergic children, 571

WEST, EDWARD J. (WITH BOOHER, CRAIG E., AND FARRELL, JAMES B.), Pertussis: clinical comparison of the newer antibiotics, 411

WILHELM, HAZEL S. (WITH SOBEL, IRWIN PHILIP), The role of the Rh factor in the etiology of cerebral palsy, 447

WINKLEY, RUTH, JACKSON, KATHERINE, FAUST, OTTO A., MURRAY, MARJORIE F., AND CERMAK, ETHEL G., Emotional reactions and behavior of children in the home, 476

WOODING, CLINTON H., AND SCOTT, ROLAND B., Terramycin in treatment of pneumonias of childhood, 423

WRIGHT, LYDIA, AND JENKINS, SAMUEL, Erythema multiforme exudativum, 310

Z

ZALEZNAK, BERNARD D. (WITH FELDMAN, SAMUEL, GOODGOLD, JOSEPH, AND LEVY, HAROLD), Acute thrombosis of the femoral artery in an infant, 498

— (WITH KAUFMAN, BENJAMIN, LEVY, HAROLD, AND LITVAK, ABRAHAM M.), Statistical analysis of 242 cases of meningococcus meningitis, 705

ZWEIFLER, BEN M. (WITH ROSENBLATT, PHILIP), Type f Hemophilus influenzae meningitis, 620

— (WITH STERNBERG, S. DAVID, AND HOFFMAN, CHARLES), Stomatitis and diarrhea in infants caused by Bacillus mucosus capsulatus, 509

— (WITH STERNBERG, S. DAVID, GRUBER, SEYMOUR, AND LICHTERMAN, JACOB), The Shwartzman phenomenon complicating acute meningococcemia with meningitis, 369

SUBJECT INDEX*

A

Abdominal pain as manifestation of epilepsy (abdominal epilepsy) in children (Livingston), 687
Adrenocorticotropic hormone and thymectomy in lymphatic leucemia (Earle et al.), 63
  some observations on use of, in topic dermatitis in infancy (DiGeorge and Nelson), 164
Adoption practices, current (Amatruda and Baldwin), 208
Agenized flour products, variation of, in diet, clinical study in man of effects of (Laufer et al.), 341
Allergy management, effect of, on growth and development of allergic children (Welsh), 571
Anal papillae, anomalous, in infants and children (Nichamin and Kallet), 468
Antibiotics, newer, clinical comparison of, for pertussis (Booher et al.), 411
  treatment of infantile diarrhea with new combination of (Kadison and Borovsky), 576
Aortic arch, unusual anomaly of (Goldwyn), 442
  atresia with hypoplasia of left heart and aortic arch (Friedman et al.), 354
Astoria plan: decade of progress (Jacobziner), 221
Atopic dermatitis in infancy, some observations on use of adrenocorticotropic hormone in (DiGeorge and Nelson), 164
  penicillin sensitivity simulating (Cohen), 741
Aureomycin, Hemophilus influenzae pyarthrosis and meningitis treated with (Joslin and Howard), 375
  in pediatrics: review (Shwachman et al.), 91
  ineffectiveness of, in preventing primary vaccinia reaction (High and Reiner), 60
  intravenous, Salmonella bareilly meningitis in a child successfully treated with (Padnos and Goldin), 85
  treatment of localized Pasteurella multocida infection with (Neter et al.), 242
Auricular septal defects in children (Keith and Forsyth), 172

B

Bacillary dysentery in infancy and childhood, clinical evaluation of streptomycin in treatment of (Chang and Su), 602
Bacillus mucosus capsulatus, stomatitis and diarrhea in infants caused by (Sternberg), 509
Behavior, children's, pediatrician and his role in understanding (Mercer), 525
  emotional reactions and, of children in home (Winkley et al.), 476
  later, relationship between infant feeding experience and (Newton), 28
Biolac, value of, clinical study concerning, effect of changes introduced in New Improved Biolac upon growth of young infants (Hazard et al.), 18
Book Reviews:
  A manual of cerebral palsy equipment, 272
  An atlas of human anatomy (Anson), 271
  Diseases of the endocrine glands (Oswald), 272
  Endocrine disorders in childhood and adolescence (Wilkins), 406
  Handbook of biolinguistics (Meader and Muyskens), 532
  Love is not enough (Bettelheim), 144
  Methods in medicine (Herrmann), 407
  Microphthalmos and anophthalmos with or without coincident oligophrenia (Sjögren and Larsson), 272
  Modern trends in pediatrics (Parsons, ed.), 779
  Nutrition in health and disease (Cooper et al.), 272
  Pathologic physiology: mechanisms of disease (Sodeman, ed.), 271
  Pediatric x-ray diagnosis (Caffey), 780
  Psychosomatic medicine: its principles and applications (Alexander), 407
  Public health is people (Ginsburg), 407
  Speech problems of children (Johnson, ed.), 144
  Teaching the retarded child at home (Osterhout), 271
  The pharmacological basis of penicillin therapy (Beyer), 779
  The prognosis of exudative pleurisy in children (Nathhorst), 407
  The rhesus danger: its medical, moral and legal aspects (McCurdy), 408
  Year book of pediatrics, 1950 (Poncher and Richmond, eds.), 408

*January, pp. 1-146; February, pp. 147-274; March, pp. 275-410; April, pp. 411-536; May, pp. 537-666; June, pp. 667-782.

Breast feeding, modern concept of (Levine), 472
Bulbar paralysis, frequency of, 1944-1949, tonsillectomy and poliomyelitis (Siegel et al.), 548

C

Carbohydrate-phosphoric acid solution, evaluation of, in management of vomiting (Bradley et al.), 41
Celiac disease treated with polyoxyethylene sorbitan monooleate (Boyd and Helfrick), 493
Cerebral hemispheres, total absence of (Johnson et al.), 69
palsy, role of Rh factor in, etiology of (Sobel and Wilhelm), 447
significance of delayed development in diagnosis of (Denhoff and Holden), 452
Cerebrospinal fluid and serum of infants and children, occurrence of lysozyme in (Rabe and Curnen), 147
Chart on eruption of deciduous teeth for pediatrician's office (Meredith), 482
Chloroquine, study of prophylactic value of, in children (Poindexter), 169
Clinical Conferences:
Raymond Blank Memorial Hospital for Children, Des Moines, Iowa: clinic on congenital cystic disease of lung, 511; tetanus, 515; transfusion reaction—dangerous universal donor, 518; Waterhouse-Friderichsen syndrome (?) with recovery, 522
St. Louis Children's Hospital: clinic on hypereosinophilia with eosinophilic granuloma of liver associated with ascaris infestation, 635; jejunal polyposis with intussusception and melanin spots, 641; mediastinal emphysema, pneumothorax, and subcutaneous emphysema complicating kerosene poisoning, 646
Comments on Current Literature:
congenital damage of nervous system by arthropod-borne encephalitis virus, 402
infectious mononucleosis, 267
polymyxin in treatment of meningitis due to Pseudomonas aeruginosa, 530
retrolental fibroplasia, 661
sacrococcygeal teratomas, 776
vesicular stomatitis virus of cattle producing human disease, 141
Congenital heart diseases:
aortic atresia with hypoplasia of left heart and aortic arch (Friedman et al.), 354
auricular septal defects in children (Keith and Forsyth), 172
congenital valvular pulmonary stenosis with or without interatrial communication: physiologic studies as diagnostic aids (Adams et al), 431
unusual anomaly of aortic arch (Goldwyn), 442
Correspondence, 404, 663
Cortical excision, treatment of epilepsy by (Walker), 285
Cystic disease of lung, clinic on (Raymond Blank Memorial Hospital for Children), 511

D

Diabetics, juvenile, later status of (Daeschner et al.), 8
Diaphyseal dysplasia, progressive (Engelmann's disease) (Gillespie and Mussey), 55
Diarrhea and stomatitis in infants caused by Bacillus mucosus capsulatus (Sternberg et al.), 509
epidemic, of infancy (Rubenstein and Britten), 457
infantile, treatment of, with new combination of antibiotics (Kadison and Borovsky), 576
Dysplasia, diaphyseal, progressive (Gillespie and Mussey), 55
ectodermal, hereditary (Ellingson), 191

E

Editor's Column:
antihistaminic drugs and common cold. II., 534
"Courrier," 409
new Journal format, 410
number and distribution of pediatricians, 273
paralytic poliomyelitis following immunizing injections, 781
pediatrics and psychiatry, 409
research, 666
tuberculous meningitis, 145
Electrocardiographic changes occurring during course of replacement transfusions (Furman et al.), 45
Emotional reactions and behavior of children in home (Winkley et al.), 476
Emphysema, mediastinal, pneumothorax, and subcutaneous emphysema complicating kerosene poisoning, clinic on (St. Louis Children's Hospital), 646
Encephalitis virus, arthropod-borne, congenital damage of nervous system by (Blattner), 402
Engelmann's disease (Gillespie and Mussey), 55
Eosinophilic granuloma, hypereosinophilia with, of liver associated with ascaris infestation, clinic on (St. Louis Children's Hospital), 635
Epilepsy in children, abdominal pain as manifestation of (Livingston), 687
treatment of, by cortical excision (Walker), 285
Erythema multiforme as manifestation of neonatal septicemia (Starr and Holliday, Jr.), 315
exudativum (Wright and Jenkins), 310

F

Feeding, breast, modern concept of (Levine), 472
experience, infant, and later behavior, relationship between (Newton), 28
infant, artificial, new suckling device for (Hawkins), 484
of premature infants (Hardy and Goldstein), 154
Fibroplasia, retrolental (Blattner), 661; (Exline and Harrington), 1

G

Glomerulonephritis, acute, impetigo as etiological factor (McCullough et al.), 346
Growth and development of allergic children, effect of allergy management on (Welsh), 571

H

Hemangioma associated with thrombocytopenic purpura (Southard et al.), 732
Hematoma, hygroma, and hydroma, subdural, in infants (Kinley et al.), 667
Hemolytic disease of newborn in dizygotic twins, interesting family history (Kelly and Shaffer), 717
Hemophilus influenzae pyarthrosis and meningitis treated with aureomycin (Joslin and Howard), 375
Hemorrhagic renal infarction in infancy, thrombosis of inferior vena cava and renal veins with (Feriozi et al.), 235
Hemorrhagic-necrotic skin reaction, local, following penicillin (Rubens), 630
Hereditary ectodermal dysplasia, major (Ellingson), 191
Histoplasmin skin testing in children from St. Louis, Mo., area, results of (Lynch and Alpern), 51
Hydrocephalus, internal, surgical treatment of, review of (Jackson), 251
Hygroma, hydroma, and hematoma, subdural, in infants (Kinley et al.), 667
Hypereosinophilia with eosinophilic granuloma of liver associated with ascaris infestation, clinic on (St. Louis Children's Hospital), 635
Hyperplasia, lymphoid, ileocecal intussusception caused by (O'Sullivan and Child, III), 320
Hyperthyroidism, treatment of, with radioactive iodine (Forbes and Perley), 158

I

Immunization, multiple, prenatal (Cohen et al.), 696
Impetigo as etiological factor in acute glomerulonephritis (McCullough et al.), 346
Infancy and childhood, bacillary dysentery in, clinical evaluation of streptomycin in treatment of (Chang and Su), 602
atopic dermatitis in, some observations on use of adrenocorticotropic hormone in (DiGeorge and Nelson), 164
epidemic diarrhea of (Rubenstein and Britten), 457
hemorrhagic renal infarction in, thrombosis of inferior vena cava and renal veins with (Feriozi et al.), 235
Infant, acute thrombosis of femoral artery in (Feldman et al.), 498
feeding, artificial, new suckling device for (Hawkins), 484
experience and later behavior, relationship between (Newton), 28
"Infantile insomnia," management of (Anderson), 394
Infants and children, anomalous anal papillae in (Nichamin and Kallet), 468
determination of sodium^{24} "space" in (Perley et al.), 299
occurrence of lysozyme in cerebrospinal fluid and serum of (Rabe and Curnen), 147
sinobronchitis in (Price), 590
subdural hematoma, hygroma, and hydroma in (Kinley et al.), 667
young, effect of changes introduced in New Improved Biolac upon growth of (Hazard et al.), 18
Insomnia, infantile, management of (Anderson), 394
Interview techniques in child psychiatry (Caplan), 128
Intracranial calcification following pneumococcic meningitis (Levinson and Hartenstein), 624
Intussusception and melanin spots, jejunal polyposis with, clinic on (St. Louis Children's Hospital), 641
ileocecal, caused by lymphoid hyperplasia (O'Sullivan and Child, III), 320

J

Jejunal polyposis with intussusception and melanin spots, clinic on (St. Louis Children's Hospital), 641

K

Kerosene poisoning, mediastinal emphysema, pneumothorax, and subcutaneous emphysema complicating, clinic on (St. Louis Children's Hospital), 646

L

Leucemia, lymphatic, thymectomy and ACTH in (Earle et al.), 63
Lung, congenital cystic disease of, clinic on (Raymond Blank Memorial Hospital for Children), 511
Lysozyme, occurrence of, in cerebrospinal fluid and serum of infants and children (Rabe and Curnen), 147

M

Medical Progress:
aureomycin in pediatrics: review (Shwachman et al.), 91
evolution of systemic reticuloendotheliosis in childhood (Freud), 744
review of surgical treatment of internal hydrocephalus (Jackson), 251
urologic considerations in pediatrics (Campbell), 387
Meningitis and Hemophilus influenzae pyarthrosis treated with aureomycin (Joslin and Howard), 375
due to Pseudomonas aeruginosa, polymyxin in treatment of (Blattner), 530
meningococcus, statistical analysis of 242 cases of (Kaufman et al.), 705
pneumococcic, intracranial calcification following (Levinson and Hartenstein), 624
Salmonella bareilly, in child successfully treated with intravenous aureomycin (Padnos and Goldin), 85
type f Hemophilus influenzae (Rosenblatt and Zweifler), 620
Meningococcemia, acute, with meningitis, Shwartzman phenomenon complicating (Sternberg et al.), 369
Methemoglobinemia in premature infants caused by marking ink, methylene blue in treatment of (Etteldorf), 24
Methylene blue in treatment of methemoglobinemia in premature infants caused by marking ink (Etteldorf), 24
Mononucleosis, infectious (Blattner), 267
Mother-pediatrician relationship in neonatal period (Carithers), 654

N

Neonatal septicemia, erythema multiforme as manifestation of (Starr and Holliday, Jr.), 315
Nervous system, congenital damage of, by arthropod-borne encephalitis virus (Blattner), 402
Neuroblastoma sympatheticum with metastases (Goldring), 231
Neuroses, prevention of (Lott), 259
Newborn, hemolytic disease of, in dizygotic twins, interesting family history (Kelly and Shaffer), 717
Salmonella infections of (Epstein et al.), 723
News and notes, 143, 269, 405, 532, 664, 778
Nursery, recovery, function of, in large maternity hospital (Bloxsom), 618

O

Osteomyelitis, Salmonella typhimurium (Traisman and Champlin), 244

P

Pasteurella multocida infection, localized, treatment with aureomycin (Neter et al.), 242
Pediatrician and his role in understanding children's behavior (Mercer), 525
Pediatrician-mother relationship in neonatal period (Carithers), 654
Penicillin, local hemorrhagic-necrotic skin reaction following (Rubens), 630
sensitivity simulating atopic dermatitis (Cohen), 741
Periostitis, traumatic, in young children (Barmeyer et al.), 184
Personality investigation of children, projective tests in (Halpern), 770
Pertussis: clinical comparison of newer antibiotics (Booher et al.), 411
Pneumoencephalography, technique of, in children: comparative results with air and oxygen injection (Casamajor et al.), 463
Pneumonias of childhood, terramycin in treatment of (Wooding and Scott), 423
Poisoning, kerosene, mediastinal emphysema, pneumothorax, and subcutaneous emphysema complicating, clinic on (St. Louis Children's Hospital), 646
Poliomyelitis in early neonatal period: report of case of possible intrauterine infection (Shelokov and Weinstein), 80
tonsillectomy and, frequency of bulbar paralysis, 1944-1949 (Siegel et al.), 548
studies on incidence in 1949 (Siegel et al.), 537
Polymyxin in treatment of meningitis due to Pseudomonas aeruginosa (Blattner), 530
Polyoxyethylene sorbitan monooleate, celiac disease treated with (Boyd and Helfrick), 493
Pregnancy, illness in first trimester of, its lack of significance in relation to congenital anomaly of offspring and to full-term pregnancy, prematurity, and stillbirth (Hartman and Kennedy), 306
Premature infants, feeding of (Hardy and Goldstein), 154
methemoglobinemia in, caused by marking ink, methylene blue in treatment of (Etteldorf), 24
Projective tests in personality investigation of children (Halpern), 770
Pseudomonas aeruginosa, meningitis due to, polymyxin in treatment of (Blattner), 530
Psychiatry, child, some interview techniques in (Caplan), 128
pediatrician looks at (Porter), 275
Psychologic Aspects of Pediatrics:
management of "infantile insomnia" (Anderson), 394
mother-pediatrician relationship in neonatal period (Carithers), 654
pediatrician and his role in understanding children's behavior (Mercer), 525
prevention of neuroses (Lott), 259

Psychologic Aspects of Pediatrics—Cont'd
projective tests in personality investigation of children (Halpern), 770
some interview techniques in child psychiatry (Caplan), 128
Pulmonary stenosis, valvular, congenital, with or without interatrial communication: physiologic studies as diagnostic aids (Adams et al.), 431
Pyarthrosis, Hemophilus influenzae, and meningitis treated with aureomycin (Joslin and Howard), 375

R

Radioactive iodine, treatment of hyperthyroidism with (Forbes and Perley), 158
Rathke's pouch (Johnson and Meredith), 380
Reticuloendotheliosis, systemic, evolution of, in childhood (Freud), 744
Rh factor, role of, in etiology of cerebral palsy (Sobel and Wilhelm), 447
problem in mixed racial group, survey of (Pomerance and Salerno), 349
Rooming-in program, elective, experiences with (Pennoyer), 213

S

Salmonella bareilly meningitis in child successfully treated with intravenous aureomycin (Padnos and Goldin), 85
infections of newborn infant (Epstein et al.), 723
typhimurium osteomyelitis (Traisman and Champlin), 244
Sexual development, precocious (Lowrey and Brown), 325
Shwartzman phenomenon complicating acute meningococcemia with meningitis (Sternberg et al.), 369
Sickle-cell disease, report of case with anemia, subarachnoid hemorrhage and cerebral thrombosis (Bloch et al.), 88
Sinobronchitis, childhood, chronic, treatment program for (Price and Binns), 597
in infants and children (Price), 590
Situs inversus (Tanner-Cain and Crump), 199
Sodium^{24} "space," determination of, in infants, children, and adults (Perley et al.), 299
Stomatitis and diarrhea in infants caused by Bacillus mucosus capsulatus (Sternberg et al.), 509
vesicular, virus of cattle producing human disease (Blattner), 141
Streptomycin, clinical evaluation of, in treatment of bacillary dysentery in infancy and childhood (Chang and Su), 602
Suckling device, new, for artificial infant feeding (Hawkins), 484
Suprasellar (Rathke's pouch) cyst (Johnson and Meredith), 380
Syringe, self-lubricating (Bloxsom), 491

T

Teeth, deciduous, eruption of, chart on, for pediatrician's office (Meredith), 482
Teratomas, sacrococcygeal (Blattner), 776
Terramycin in treatment of pneumonias of childhood (Wooding and Scott), 423
of typhoid fever (Reilly and Earle), 428
Tetanus, clinic on (Raymond Blank Memorial Hospital for Children), 515
Thrombocytopenic purpura, hemangioma associated with (Southard et al.), 732
Thrombosis, acute, of femoral artery in infant (Feldman et al.), 498
of inferior vena cava and renal veins with hemorrhagic renal infarction in infancy (Feriozi et al.), 235
Thymectomy and ACTH in lymphatic leucemia (Earle et al.), 63
Tonsillectomy and poliomyelitis, frequency of bulbar paralysis, 1944-1949 (Siegel et al.), 548
studies on incidence in 1949 (Siegel et al.), 537
Tracheo-esophageal fistula, congenital, without esophageal atresia (Helmsworth and Pryles), 610
Transfusion reaction—dangerous universal donor, clinic on (Raymond Blank Memorial Hospital for Children), 518
Transfusions, replacement, electrocardiographic changes occurring during course of (Furman et al.), 45
Turner's syndrome, case of (Cunningham and Harley), 738
Twin fetuses in fetu (Gross and Clatworthy, Jr.), 502
Typhoid fever, terramycin in treatment of (Reilly and Earle), 428

U

Urologic considerations in pediatrics (Campbell), 387

V

Vaccinia reaction, primary, ineffectiveness of aureomycin in preventing (High and Reiner), 60
Vomiting, carbohydrate-phosphoric acid solution in management of, evaluation of (Bradley et al.), 41

W

Waterhouse-Friderichsen syndrome (?) with recovery, clinic on (Raymond Blank Memorial Hospital for Children), 522
Werner's syndrome, juvenile type of (Shelby and Vaughn), 559

CONTENTS FOR JUNE, 1951

Original Communications

Subdural Hematoma, Hygroma, and Hydroma in Infants. Gordon Kinley, M.D., Harris D. Riley, Jr., M.D., and Claude S. Beck, M.D., Cleveland, Ohio ---- 667

Abdominal Pain as a Manifestation of Epilepsy (Abdominal Epilepsy) in Children. Samuel Livingston, M.D., Baltimore, Md. ---- 687

Prenatal Multiple Immunization. Philip Cohen, M.D., Herman Schneck, M.D., and Emanuel Dubow, M.D., New York, N. Y. ---- 696

Statistical Analysis of 242 Cases of Meningococcus Meningitis. Benjamin Kaufman, M.D., Harold Levy, M.D., Bernard D. Zaleznak, M.D., and Abraham M. Litvak, M.D., Brooklyn, N. Y. ---- 705

Hemolytic Disease of the Newborn in Dizygotic Twins: An Interesting Family History. James J. Kelly, M.D., and James G. Shaffer, Sc.D., Louisville, Ky. ---- 717

Salmonella Infections of the Newborn Infant. Harold C. Epstein, M.D., Adolf Hochwald, M.D., and Rosemary Ashe, M.T., Cleveland, Ohio ---- 723

Case Reports

Hemangioma Associated With Thrombocytopenic Purpura. Samuel C. Southard, M.D., Adolph G. DeSanctis, M.D., and Robert J. Waldron, M.D., New York, N. Y. ---- 732

A Case of Turner's Syndrome. Guy C. Cunningham, M.D., and John F. Harley, M.D., Louisville, Ky. ---- 738

Penicillin Sensitivity Simulating Atopic Dermatitis. Sheldon G. Cohen, M.D., Wilkes-Barre, Pa. ---- 741

Medical Progress

Evolution of Systemic Reticuloendotheliosis in Childhood. Paul Freud, M.D., New York, N. Y. ---- 744

Psychologic Aspects of Pediatrics

Projective Tests in the Personality Investigation of Children. Florence Halpern, M.A., New York, N. Y. ---- 770

Comments on Current Literature

Sacrococcygeal Teratomas. Russell J. Blattner, M.D., Houston, Texas 776

News and Notes

News and Notes ---- 778

Book Review

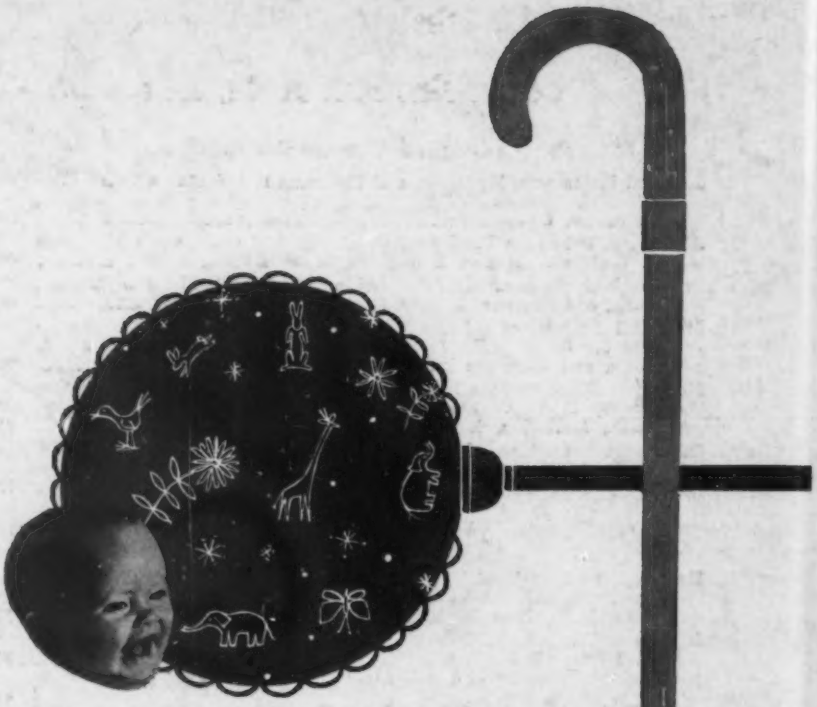
Book Reviews ---- 779

Editor's Column

Paralytic Poliomyelitis Following Immunizing Injections ---- 781

Index

Index ---- 783



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